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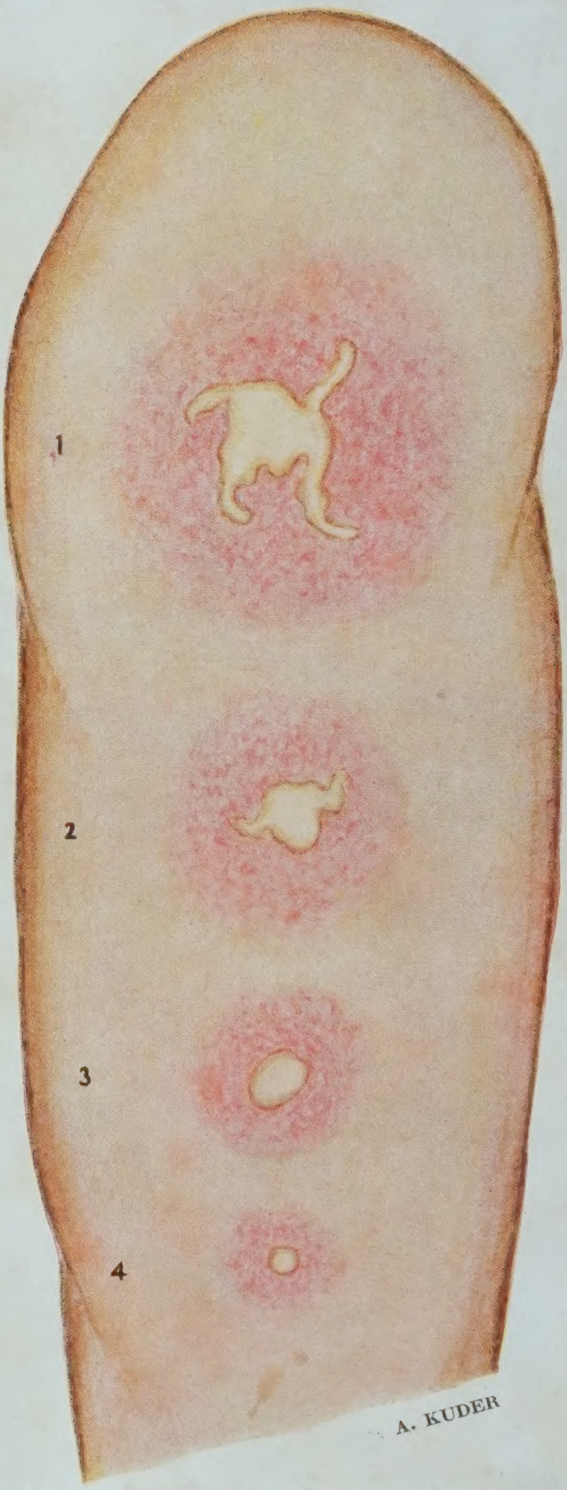

Intradermal skin tests showing immediate wheal type reactions. Drawn from life within fifteen to twenty minutes after the tests were made. 1, Marked active (++++). 2, Marked (+++). 3, Moderate (++). 4, Slight (+).

ALLERGY

in Theory and Practice

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FOREWORD

Medical Education and Allergy

Instruction in medicine is admittedly becoming more difficult to plan and it is still harder for the student to acquire a completely rounded education on account of the steadily increasing amount of material that must be absorbed. The guiding principle, therefore, in the allocation of subject-time must be on the basis of relative importance, and this is no mean task in the limited time available in the usual four-year medical curriculum, now reestablished.

Instruction in allergy has lagged in spite of its steadily increasing importance as evidenced by its basic significance and broad applicability in the theory and practice of medicine and its various subdivisions. It is my aim to indicate how this deficiency may be corrected at the undergraduate, graduate and post-graduate level without too great disturbance to existing plans or ideas.

First, then, with regard to *undergraduate instruction:* Allergy is an essential part of the basic sciences of immunology, bacteriology, pathology, pharmacology and physiology. Immunology cannot be taught without a discussion of sensitization in the experimental animal (anaphylaxis) and in man; therefore during the course a lecture, or preferably two, could be given on the principles of this phenomenon with some reference to its applicability in human disease. This, supplemented by extra laboratory demonstrations of shock and of precipitin, of the Schultz-Dale reaction and of passive transfer skin tests, would form the basis on which the study of allergy could be gradually developed throughout the student years. The teaching of pathology including the mechanism of tissue reaction would be incomplete without reference to the anatomic-pathologic aspects of the allergic reaction as ably presented by Dr. Klemperer in Chapter 4, nor can pharmacology be adequately covered without mention and explanation of the increasingly important drug allergies, for it will not suffice to call them "idiosyncrasies" as has been done over the years past without any attempt at interpretation.

So by working the subject of allergy into these basic courses in the early years of his medical study, the student comes to his clinical work with a foundation that permits a ready grasp of those various diseases for which allergic reactions, in whole or in part, are responsible. In the third or fourth year a few lectures, possibly four, on allergic diseases should suffice to coordinate the basic facts and theories with clinical diseases such as tuberculosis, syphilis, rheumatic fever and those of the erythema group, as well as asthma, urticaria, serum disease and the manifestations of drug allergy. Then in addition, when the student is in the ward or outpatient service as a clinical clerk, an occasional case should be assigned in order to bring out the important points of an adequate allergy history, to demonstrate the special technics and to discuss the interpretation of skin tests.

All of the work that I have indicated could be covered fairly adequately in a total of some eight to ten hours, I believe, at no sacrifice, indeed rather with advantage to other important subjects. Actually the lack of allergy training in many of the medical schools can be directly attributed to the fact that there has been no one on the staff adequately interested to integrate the subject with the basic fields or prepared to teach students the grade of clinical allergy I believe could and should be taught.

Graduate instruction divides itself into the early years of intern training and the later extended work in residencies and fellowships. The usual two years of medical *internship* should be devoted primarily to the basic field of internal medicine or pediatrics, but a rotation, possibly by election, through the various clinics dealing with the medical subspecialties as allergy, diabetes, hematology and cardiology would exert a wholesome and broadening influence. In a properly organized allergy department an intern could profitably spend one or two months and gain clinical and technical experience of great value, particularly useful for those who go immediately into general practice where problems in allergy will present themselves in at least 7 to 10 per cent of the patients. Physicians so trained will know how to undertake the study and treatment of such cases at least in their simpler form. With an occasional short and properly sponsored post-graduate course of the "refresher" type which is available, these practitioners will be able to render greater and more capable service to their communities.

For those fortunate enough to be able to extend their graduate training as *Residents* or *Fellows* for a longer period with the ultimate object of teaching or research or of acquiring specialty status by certification in the shortest possible time, another year of internal medicine is a great advantage though not always feasible before venturing into any subspecialty field. I speak of allergy as the one most familiar to me, but these three years of internal medicine as intern and resident give an excellent background for special training in this field. Allergy should appeal to the young physician at this stage of his career not only because of the opportunities and the need for men with this experience but because of its importance and the interesting problems inherent in the subject. Two years in a fellowship or residency in allergy while continuing contacts with internal medicine afford opportunity for experience in the immunologic, pathologic, bacteriologic and chemical phases of allergy in addition to clinical work. Such physicians trained in medicine or pediatrics are then eligible for certification examination by the appropriate and officially recognized American Board, and should be ready to assume a responsible position in medical practice, teaching and research. It is worth noting, however, that no time should be spent with any institution in which the residencies in medicine and allergy have not been "approved" by the Council on Medical Education of the American Medical Association.

The purposes of the various American Boards have been high and to a large extent their aims have been accomplished in advancing education and stimulating the efforts of physicians to improve their knowledge. But the Boards in no way desire to regiment or restrict the proper activities of physicians. A practitioner can conduct a successful practice without certification and certification does not guarantee that a man will be a good doctor. It is merely the badge of acquired knowledge through extended training.

The widespread demand by practicing physicians for *post-graduate* instruction in allergy is evidenced by the enrollment at each and every course offered. The reason for this is attributable to the lack of such instruction during medical school and hospital intern years, and to the need for such information because of the frequency with which allergy problems are met in general or medical or pediatric practice.

Several types of course might be suggested to satisfy this demand but essentially they resolve themselves into a short one- or two-week period and a longer one of several months. The aims of these courses should be strictly defined, the subject matter reliably set forth and the sponsorship must be above reproach.

In a short one- or two-week course it is possible to present the established and accepted facts of allergy in a simple manner, and methods of diagnosis and treatment and their limitations can be given with and without illustrative cases and supplemented by colloquia. Practicability is of the essence in such a course for physicians in general medicine. It is not a course in preparation for specialization.

Longer courses of several months' duration should be made available more generally than is now possible on account of the lack of adequately trained instructors. This type of work is possible only on the smallest scale for physicians who have opportunity to attach themselves as volunteers to one of several allergy units where teaching, research and clinical facilities are at hand. Such work, if continued with study and practice, might well be a stepping stone to certification if the basic training in medicine or pediatrics meets the requirements of the proper Boards.

I hope in this note on education in allergy I have been able to make clear that the existing training facilities are not adequate, and at the same time to indicate what I think the aims and purposes should be. I may likewise express the hope that this book will afford in its presentations and its references material that will be a help in self-education.

Robert A. Cooke

PREFACE

In its extensive program of postgraduate instruction, The American College of Physicians has sponsored short courses in allergy for some years past, several of which it was my privilege to organize with the able assistance of many of those I like to think of as members of "our New York group." This book is the ultimate outcome of such a cooperative venture in postgraduate teaching and presents, though more fully and formally than was possible in the didactic lectures, the theoretical and practical instruction given during these courses.

The aim of this volume is to record the facts of allergy and, further, to synthesize them into a body of knowledge in so far as this is possible today, realizing fully the existing limitations of information and possible errors of interpretation. It has been our hope and our endeavor to make this book a useful one to those interested in the practical application of allergy in general practice and to students of allergy as well as to the scientifically minded who find allergy an alluring subject on account of the intricacies of its immunologic phases.

I wish to acknowledge fully my appreciation of the sympathetic assistance of the contributors, many of whom have been in the past or now are my associates in my own organization which began in 1919 at the New York Hospital and has continued from 1932 at the Roosevelt Hospital. It is not possible to express in words my indebtedness to another group of my associates, Drs. Barnard, Bengtsson, Boker, Hampton, Loveless, Sherman, Stull and Wing, through whose work and from whose ideas I have so largely profited through the years. Many of them, had they not been in active service as medical officers with the armed forces during the war, would have been contributors to this book.

Throughout the various chapters serious effort has been made to give adequate credit by reference to the many students of allergy whose ideas and observations have been previously published. I can only apologize for any errors or omissions.

I have been greatly helped by the critical review of Chapter 3 on Serologic Features of the Allergic Reaction by Dr. Sanford Hooker, Chapters 13 and 14 on Allergic Dermatitis by Dr. George Andrews and Dr. Chester Fraser, Chapter 19 on Allergic Neuropathies by Dr. Foster Kennedy and Dr. Lewis Stevenson, and Chapter 21, Allergy of the Eye, by Dr. Townley Paton, also by the review and helpful advice throughout the book of my associate, Dr. William B. Sherman.

I wish to acknowledge my gratitude to Miss Winifred Kelly whose interest and concern have never lessened during a long period of preparation. Her flair for precision in the expression of thought and meticulous accuracy of detail as to references, type and tables, could not be surpassed. Also I must express my thanks to my wife and to my secretaries, Miss McNally, Miss Brennan, Miss Egan and Miss Kuder for their ready assistance as well as their tolerance.

Finally and in particular I want to state the debt I owe to Dr. Albert Vander Veer. He and I have worked, fought and thought together as associates for over thirty happy years on every phase of allergy, scientific and practical, in its development as a separate field and in its relation to internal medicine, the organizations for its advancement and the organization of our department of allergy for treatment, for teaching and for research. No one could hope to have a more loyal adviser and supporter.

It is with a certain reluctance, considerable apprehension and a minimum of pride that I now release this brain child to my publishers with due thanks for their forbearance and courtesy and with the hope that it will fill a need and, despite shortcomings, will be of service in the interpretation of allergic diseases to the physicians and students and through them to the laity.

Robert A. Cooke

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Section I

FUNDAMENTAL ASPECTS OF ALLERGY

1. *Principles and Theory*

ROBERT A. COOKE

BASED upon the concept of sensitivity a number of human ills have been grouped together and today are generally recognized as *Diseases of Allergy*. These are asthma, allergic rhinitis of the perennial and seasonal (hay fever) type, urticaria and angioedema with cutaneous, cerebral and visceral manifestations, allergic dermatitis and allied dermatoses, serum disease and serum shock. In addition to these rather definite disease entities this sensitivity concept is increasingly employed to explain the signs and lesions of many diseases, as for example, the exanthem of scarlet fever, the arthritis of rheumatic fever and the vascular inflammation following serum and drug therapy. On account of the importance of these recent developments, as well as of the diseases of allergy as such, a new and broader significance is accruing to allergy in the field of medicine.

History

The development of the concept of allergy forms an interesting story. As a matter of fact allergy is an accidental by-product of the general use of antiserums to combat the diseases of man. In 1890 von Behring discovered diphtheria antitoxin. Within a few years following the therapeutic use of the antitoxic horse serum three effects were noted and eventually proven to be due primarily to the serum proteins and not the antitoxin, namely serum disease and serum shock in man and anaphylactic shock in animals. The discovery of diphtheria antitoxin gave impetus to the search for antiserums against other bacteria or their toxins as well as to the study of the response of the host to bacterial infection. This was all part of the beginning of the science of immunology.

Experimenting with certain toxins, Richet noted that some of his animals after receiving injections of Actinia extract became more sensitive rather than immune. In 1902 he coined the word "anaphylaxis" to designate this increased reactivity as opposed to the usual protected or immune state engendered by toxin injections.

In 1904 Theobald Smith while working with diphtheria antiserums, not toxins, noted the sudden death of guinea pigs in convulsions on reinjection of the serum ten days after the first harmless dose. To this phenomenon the word "anaphylaxis" was also applied, on account of the similarity of the symptoms to those observed by Richet with toxins, and of the conditions under which the reaction ensued. Anaphylaxis promptly became a topic of absorbing interest. Scientists by the score put forth their observations and ideas in a rapidly growing volume of literature and from the accumulated and conflicting theories and data there has emerged a certain but still limited knowledge of cause and effect.

The primary and harmless parenteral introduction of foreign protein stimulates cells of the recipient to the production of specific antibodies, some cellular and the balance humoral, that is, circulating in the blood serum, which acts as an overflow reservoir for excess antibody. It is now agreed that the Theobald Smith phenomenon of anaphylactic shock is the result of a reaction following the union of the specific cellular antibody with its antigen. This much was known twenty-five years ago and even today it is not known why certain cells respond with specific antibody production nor just which cells they are, nor can the explosive reaction called anaphylactic shock be definitely explained. Along this line some progress is being made and I shall have occasion to consider it later at greater length when histamine in relation to allergy is discussed (p. 15).

Observations of phenomena that are now recognized as allergic have been recorded throughout clinical medical literature from the earliest years. Hippocrates must have seen certain evidence that prompted his sixty-fourth aphorism: "It is a bad thing to give milk to persons having headache." The majority of the earlier medical records deal with the untoward effects of drugs in certain human beings, such effects having no relation to the usual pharmacologic action of the drug. Idiosyncrasy was the term used for these effects but no explanation was forthcoming. For untold generations mothers have recognized that certain infants were "poisoned" by cow's milk or eggs and that an occasional child had an attack of coryza or asthma after contact with animals. But physicians, their minds cloaked with the ignorance of the times, were satisfying themselves, if not their patients, with the learned diagnosis of neurosis or hysteria.

When anaphylaxis came into the picture, however, it was quickly adopted by the clinicians. Wolff-Eisner in 1906 suggested that hay fever was an example of such a phenomenon. Blackley, years before (1873), demonstrated that pollen caused hay fever but, as he did not have a name or a theory for his observations, little or no attention was paid to his faultless experiments. He was ahead of his time. He did skin and eye tests with pollen and recorded local wheal and systemic reactions in hay fever victims and only in them, just as is done today, and he showed that normal non-hay fever patients gave no reaction.

In 1909 the records of cases of prompt and sudden death after diphtheria antitoxin were collected and studied by Gillette.[1] He first called attention to the similarity of the so-called anaphylactic shock and asthma. He also noted and discussed the still more important fact that the majority of these accidents occurred in asthmatics and followed the *first*, not the second injection of horse serum (antitoxin). Meltzer[2] is frequently credited with this suggestion.

Serum disease was also quite understandably regarded as anaphylaxis for it certainly followed a parenteral injection of serum and the incubation period was identical with that for experimental anaphylactic sensitization. Urticaria, which was a prominent symptom in serum disease in human beings, was not observed in animals, hence serum disease was regarded as a special form of anaphylaxis in man. It all seemed simple, then, with urticaria, asthma and hay fever in the anaphylaxis fold.

Thus gradually was evolved the concept of an antigen-antibody reaction for the group of diseases now called allergies. The period from 1910 to 1920 was occupied with the development of empirical standards for clinical treatment, especially of hay fever and asthma, with the technic of skin testing, the discovery of new allergens, the preparation of extracts and the early attempts at their standardization. In 1921 came the outstanding development, the demonstration of a positive skin-sensitizing factor that is transferable by the serum of allergic patients to nonsensitive test subjects, this becoming known as the Prausnitz-Küstner[3] reaction. Some years later (1935) in a search for the protective mechanism to explain the clinical benefits resulting from the treatment of hay fever with pollen extracts, a specific blocking or inhibiting antibody (precipitin) was demonstrated in the blood serum of treated patients by Cooke et al.[4]

This general résumé of the scientific and clinical history of the development of the concept of allergy fails to make clear the considerable gaps in our knowledge and the contradictions that still exist both in theory and in fact. These are revealed and discussed to some extent in the pages that follow.

Incidence of Allergy

As will be seen in the later discussion, practically all human beings are capable of becoming sensitized to certain antigenic substances under certain circumstances and special conditions. In other words, antibody production is a normal cellular function. This, however, is not what is meant by allergy. The subject here is the general frequency of allergic disease—the number of persons in the general population who in the usual conduct of their lives develop allergic reactions to various and sundry substances with which they come in contact.

If one were to include the cases of ivy dermatitis and all that miscellaneous group which are today being diagnosed as allergies—allergic headache, allergic arthropathy, gastro-intestinal allergy, allergic fever, together with the allergic evidences of infectious disease, as the rash of scarlet fever, the arthritis of rheumatic fever and certain lesions of tuberculosis, to mention but a few—these together with the recognized and accepted diseases of allergy would of course make the incidence of allergy very high. The dilemma of what to include is not an easy one to solve. If one takes a liberal point of view in diagnosis and accepts the so-called minor allergies, many of which are not adequately proven, then a figure of incidence of 50 per cent as given by Vaughan[5] is certainly too low. On the other hand, if only the regularly accepted allergies—allergic coryza, seasonal and perennial asthma, the urticaria-angioedema group and the allergic dermatoses—are included, then the figure of 7 per cent as given by Cooke and Vander Veer[6] in 1916 is more nearly correct.

Nomenclature

Immunologists and students of allergy over the years have developed their own professional language by appropriating or coining words to designate allergy or special phases of it or certain components of the allergic reaction. In general the jargon of allergy is based upon the nomenclature of anaphylaxis. With the growth of the subject some words have lost their original significance entirely or they have acquired a double meaning which leads to confusion. Others have served their day and should be eliminated.

Allergy (altered reactivity) is the word coined and first used by von Pirquet[7] in 1906 to designate the alteration of reactions as he observed them occurring in persons in response to second or later injections of smallpox vaccine and of horse serum. The alteration in these cases was quantitative rather than qualitative and consisted especially of a shortening of the incubation time of the reaction. Allergy was such a short, neat and expressive word that by a sort of common consent it has been appropriated and is now generally used to designate a special group of diseases in man. On account of the interrelations of the various antigen-antibody reactions of man and of animals and the pressing need for a concise over-all word for all such reactions, "Allergy" should be selected as that word and in conformity with this generally accepted idea the following definitions are given:

The "allergic state" is one of potential reactivity of certain individuals (man or experimental animals) due to the existence of a mechanism called antibody which mediates the linkage of a substance (antigen) to those cells to which an antibody, specific for the antigen, has become attached. Excess antibody, termed *humoral*, not cellularly attached, is often present in the circulating blood and tissue fluids. Cellular antibody is spoken of as *somatic* and the cells to which the antibody is attached are termed "sensitized" cells.

Allergy is the reaction qualitatively altered from the normal when union of antigen and cellular antibody is effected. This is a broad and all-inclusive definition which could include such antigen-antibody reactions as those resulting from the transfusion of incompatible blood and other reactions not now considered and accepted as within the realm of Allergy.

Hypersensitiveness and *sensitization* are cumbersome words, but if used synonymously with "allergic state" there is no objection to them.

Hyperergia (Hyperergy). This was originally used to designate an excessive degree of physiologic or pharmacologic response, but it is now used by some to denote acute or hyperallergic reactions. This is an incorrect use of the word, which should be used, if at all, only in its original sense and as its derivation implies.

Pathergy is a word that is sometimes used. As it is essentially synonymous with the word allergy it should be dropped, since there is no particular point in its clinical use and it clutters an already overburdened nomenclature. If applied solely to the morphology of allergic reactions it might serve a useful purpose.

Idiosyncrasy has long been in use and has been applied primarily to the unusual effects of drugs in certain cases with symptoms unrelated to the pharmacologic action of the drug. It has no advantage over the present term "drug allergy" but may be used synonymously though it is preferably omitted.

Anaphylaxis has become fixed in the literature to designate primarily the reaction in experimental animals in which a state of altered reactivity has been artificially induced by a parenteral injection of protein. It is an antigen-cellular antibody reaction which, as will be shown later, is identical with the altered state of reactivity in man following serum disease. Anaphylaxis, then, is a special or particular immunologic type of induced protein (or hapten) sensitivity in man or experimental animals and may properly be considered as a subdivision of Allergy.

Atopy[8] was originally used to indicate and specify the familial or hereditary group of the spontaneously appearing allergies of man. At that time it was thought that the immediate wheal-reacting allergies and the hereditary group, so-called, were one and the same. Later studies[9] showed that infective or bacterial asthma is likewise and equally subject to the hereditary influence, but does not carry the skin-reacting factor. Today "atopy" is often used also to designate allergies of the skin-reacting type rather than those with an hereditary factor, and this is a cause of much misunderstanding. My opinion is that the hereditary feature is of little practical concern and that in speaking and writing on allergy a word is needed to designate the immediate wheal-reacting type of spontaneous allergy which the single word atopy can adequately cover. I believe it should be drafted, just as the word allergy was, to fill a definite need, otherwise it should be dropped from use to avoid further confusion.

Desensitization. The word was originally used to denote a state of unresponsiveness of the anaphylactic animal to antigen injection following a sublethal or subshocking dose of the antigen. This is a factual clinical observation without adequate serologic explanation. Actually the reasons for this lack of reaction in animals are not entirely clear today. All of the immunologic work has been done on the basis of the unitarian concept of antibody which, as will be shown, is not correct. However, clinical desensitization in man comparable to that in animals has not been obtained even after artificial serum sensitization, and certainly does not obtain in the spontaneous allergies of man. Therapeutic injections as in hay fever do not desensitize and it is incorrect to speak of "desensitizing therapy" in the allergies of man.

Hyposensitization was once suggested by me[10] to designate clinically lessened sensitiveness. It is correct if used for the clinical state only, but with present knowledge it seems preferable to speak of lessened reactivity as immunity, relative or partial to be sure, but still an immune state.

Antigen is the term applied to the substance parenterally injected to produce the anaphylactic state. Since the same substance when reinjected produced the reaction, it too was spoken of as an antigen and so the word has acquired the double meaning of a substance that generates antibody, which is correct, or a substance that reacts with antibody on the cell. This is not strictly correct but is acceptable if understood. *Reactin* or *reactogen* might be coined to indicate substances, e.g., tuberculin, that react with antibody but do not stimulate antibody formation.

Allergen was then coined as a term specially applicable to the allergies of man. Actually an allergen is relatively unimportant in generating a state of sensitization in the spontaneous allergies of man for this is already developed, but the word is established and may be used quite interchangeably with antigen to denote the reacting substances.

Reagin was devised to designate what is now known as the "skin-sensitizing antibody," present in the spontaneous allergies of man. This was done after the discovery of the Prausnitz-Küstner phenomenon and on the ground that it was a special mechanism. Since the skin-sensitizing antibodies created by serum injections in man (post-serum disease) behave like those present in the skin-sensitive spontaneous allergies, the word has lost its significance and importance and should be discarded in favor of the simple word antibody, or the descriptive phrase "skin-sensitizing antibody."

Clinical Diseases of Allergy

There are two sound reasons for grouping as allergies such apparently dissimilar diseases or manifestations as seasonal or perennial coryza, asthma, eczema, urticaria, angioedema, serum shock, serum disease and anaphylaxis. These reasons are a clinical association and a common immunologic basis.

Clinical Association has long been recognized, and is well illustrated by the case histories in a study of human sensitization by Cooke and Vander Veer[5] in 1916. A large proportion of the cases had, in addition to asthma and hay fever, past or present histories of urticaria, angioedema, eczema and many unusual food or drug reactions. The antecedent histories also disclosed a similar admixture of sensitizations in the forebears and descendants.

Immunologic Relationship rests upon the concept of an antigen-cellular antibody reaction as an explanation for the various phenomena, although the existence of an antibody has not yet been proven in many of them. Certain of the abnormal and rare drug reactions illustrate the point. In a case in which asthma is caused by animal danders and by acute respiratory infection, a not unusual combination, quinine or acetylsalicylate may also produce the same asthmatic reaction. No antibody to the drug is proven by test in the skin nor is one found in the blood. In spite of this absence it is not unreasonable to assume an antigen-antibody reaction as operative, and today we accept as allergies those abnormal reactions of the body to substances which under ordinary or usual circumstances produce no similar disturbances in normal persons, reactions which are not a part of the pharmacologic or metabolic action of the antigen.

The mere existence of an allergic state does not of course constitute disease. The disease is a result of the biochemical products or biophysical forces released when antigen and sensitized tissue cells unite.

Clinical Manifestations. Since it appears that any organ or cell may become reactive and respond with one or another of the pathologic or immunologic types of reaction to be described, it is obvious that the clinical evidences are many and varied. Hence there may be in the skin such allergic lesions as urticaria, edema, erythema, purpura, the allergic dermatoses, lupus and many others; and in the respiratory tract, allergic rhinitis, hyperplastic rhinitis, polyposis, sinusitis and asthma. Abdominal allergies may take the clinical form of simple indigestion, acute or chronic gastro-enteritis and colitis, or the symptoms may simulate those of an acute abdominal condition such as appendicitis, peritonitis or obstruction. Allergic reactions to bacteria, serums and drugs give rise to various changes in the vascular system including lesions identical with periarteritis nodosa. Allergies of the central and peripheral nervous system are also recognized by symptoms of various sorts such as headache, convulsions, paralysis or coma. Hepatic, ocular, renal and vesical involvements are also recognized. It is not known what it is that determines for the individual the tissue or area (shock organ) to be involved or the pathologic or immunologic form the reaction will take. But the clinical allergy must be the net result of all the variable factors and forces involved in sensitization.

Pathology. Only brief mention will be made here of the various types of tissue changes that are seen as a result of reactions that are based upon allergy. Some of them are temporary, functional and reversible while others are organic and irreversible.

In what I call the "immediate" skin-reacting type of allergy the outstanding tissue change is *edema* and *hyperemia*, a completely reversible temporary reaction. It is typically exemplified by the so-called wheal. This is the type of tissue change seen in urticaria, in angioedema, in allergic rhinitis (hay fever) and in asthma of the immediate skin-reacting type. Long-standing local edemas may eventually lead to secondary tissue hyperplasia.

In eczema and other allergic dermatoses there is an *inflammatory and exudative lesion of the cutis* which in its acute stage is apparently completely reversible, but when the condition is protracted, lichenification, edema and connective tissue overgrowth occur. *Necrosis* may develop in certain lesions of the Arthus type.

Purpura of the non-thrombocytopenic type is frequently if not entirely an allergic manifestation. Alexander and Eyermann[11] first reported several patients in whom they could produce the lesion at will by means of certain foods. Many more cases are now on record; they are not rare. I recall a case of infective asthma with attacks of hematuria. The patient noted that they always followed the use of iodides. Cystoscopic examination during an attack showed the bladder mucosa studded with purpuric areas.

Another type of lesion is seen in the *inflammatory reactions* exemplified by the positive tuberculin test and, as shown recently by Rich,[12] in the vascular lesions resulting from protein and drug allergy.

In allergy there are therefore included such various lesions as the edematous, hyperemic, exudative, productive, necrotic, ulcerative and purpuric. It is not known what determines the type of pathology, the reaction area, the immunologic mechanism and the allergen for the individual case. It is obvious that the disease itself is the expression of the reaction once the variable factors of sensitization in the particular person have become operative and contact with the allergen is established.

Eosinophilic granulation in tissue cells and white blood corpuscles is becoming more generally recognized as an evidence of an allergic response and hence of significance in allergy. The question of to what extent and how allergy is responsible is not yet settled. As Campbell[13] has recently said, it "invariably accompanies local anaphylaxis and may or may not be evident in the general circulation." Blood eosinophilia is the rule in many immediate allergies to foods and inhalants. It is most conspicuous in many bacterial allergies but is rare in simple urticaria and angioedema of the delayed type. Eosinophilia is also present in tissue reactions such as the test wheal, the membrane of hyperplastic sinusitis and the bronchial mucosa. The source and nature of the granules is not yet known, but Cooke[8] presented evidence that they are of histogenous origin and are later ingested by all types of phagocytic cells.

Etiology. *Pathogenesis.* When the causes of the development of human sensitization are discussed one must bear in mind the different pathologic, immunologic and clinical types of allergy previously described; what holds for one may not and frequently does not hold for another. Our knowledge of these problems is limited and is not conclusive. The probable reasons or causes for the development of a sensitized state may be classified and discussed on the basis of present knowledge and ideas as (1) contact stimulation, (2) heredity, and (3) the direct or indirect effects of bacterial infection.

(1) CONTACT STIMULATION. (*a*) Physiologic Allergy: In all *artificially* produced states of sensitization quite obviously contact with the antigen is the factor responsible for the stimulation of cellular antibody. In man, horse serum when injected therapeutically in sufficient amounts produces serum disease in, roughly, 90 per cent of those so treated.[14] When the attack has subsided those patients, if skin tested directly with horse serum, give an immediate cutaneous reaction of the wheal type. Their serums contain specific precipitins as well as antibodies that will sensitize smooth muscle, as demonstrated by the Schultz-Dale reaction in the guinea pig, and also antibodies that sensitize normal human skin (Prausnitz-Küstner reaction). In the guinea pig and rabbit an anaphylactic state is produced by the parenteral injection of foreign protein in an exactly similar fashion, and the same three antibodies (precipitin, muscle-sensitizing and skin-sensitizing) are found in their serum as a result of the injection.

Another example of contact stimulation of antibody is observed in the studies on tuberculosis. A positive tuberculin test is obtained in practically all human beings or animals infected with the tubercle bacillus, whereas the uninfected do not react. Injections of tuberculin do not stimulate cells to react to tuberculin, but nearly 75 per cent of the children given injections of a suspension of heat-killed virulent (bovine) tubercle bacilli are reported by Flahiff[15] to have developed tuberculin reactions persisting up to three years. This response to tuberculin is admittedly an allergic reaction but of a different type from that stimulated by horse serum for the reaction is delayed, not prompt, the lesion is inflammatory, not an edematous wheal, and no sensitizing or precipitating antibody is found in the blood serum. For years some mechanism to mediate the reaction was hypothesized and recently Chase[16] has demonstrated the existence of a cellular antibody, for sensitization to tuberculin has been passively transferred to the guinea pig by the washed cells of a tuberculous peritoneal exudate.

A further example should be cited not only because it supports the thesis of contact stimulation, but also because it illustrates a still different type of allergy, i.e., sensitization to the oil of ivy, producing dermatitis venenata. Spain[17] showed that while infants tested with the oil were not sensitive, 75 per cent of the adults tested were reactive. Low[18] produced a typical dermatitis following the second patch test with primula when the first had been negative. Straus[19] tested day-old infants with ivy oil and, as Spain found, they were nonreactive. When he retested them a few weeks later 75 per cent were reactive. The oil itself was not irritative, as shown by the primary negative test, but a state of sensitization had been created by the first contact. Here, as in tuberculin allergy, the reaction is delayed and the mediating antibody is assumed to be cellular, for antibody has not been demonstrated in the blood serum.

Thus there are several definite examples of sensitization specifically induced in animal and man by previous contact with an antigen. They represent allergic responses which differ not only clinically but also as to their immunologic basis and their histopathology. However, since a large majority of the genus Homo respond with a reaction typical for each antigen, it may be concluded that sensitization to horse serum, tubercle bacilli and oil of ivy is a normal response for mankind. Hence these may be termed *physiologic* or *normal* types of induced allergy, because they can be produced at will on contact with these particular antigens in the majority of human beings tested. Hereditary factors apparently play no part.

(*b*) Spontaneous Allergy. The evidence just cited for contact stimulation in the production of certain allergic states, plus the absence of any other proof or satisfying theory of genesis, has led to the further and generally accepted conclusion that all sensitizations are the result of prior contact with the allergen. A critical study of the spontaneously developed clinical allergies, such as asthma, hay fever, urticaria and dermatitis, elicits some facts that cause one to question this simple hypothesis as to the origin of the allergic states from which the diseases of allergy develop. These facts are worthy of consideration and may be summarized as follows.

Only a very small percentage of people (5 to 10 per cent) develop clinical allergy, and no one has ever yet artificially induced an active sensitization in man resulting in any of the previously mentioned clinical diseases of allergy which develop spontaneously and at varying ages, dependent to some extent upon certain inherited factors. Infants are not known to be clinically sensitive at birth and are not recorded as carrying the sensitizing antibodies of their allergic mothers, in contrast to guinea pigs born of anaphylactic mothers. But infants a few weeks to a few months old, who are or are destined to be allergic, may carry skin-sensitizing antibodies in their blood as determined by direct or passive transfer tests. These antibodies, often for as many as twenty or thirty allergens, exist years before any clinical disease has developed. This suggests at least that the basis for the ultimate allergy may be laid down by some process other than simple contact. From studies of so-called infantile eczema (see chapters on Allergic Dermatitis) multiple sensitization is demonstrable in the blood in about 50 per cent of all cases. It exists to foods and inhalant substances that usually are not provocative of clinical symptoms on contact and that have no relation to the cause of the cutaneous lesions.

If excessive contact were needed to produce a sensitization one should expect a much larger percentage of infants allergic to such commonly used foods as milk and eggs. While no actual figures are available on the number of infants reacting clinically to these foods it may be conservatively estimated at not more than one per thousand. On the other hand, there are children and infants who are found to be exquisitely sensitive to such allergens as mustard, with which there certainly is no excessive contact. But mustard cannot be considered a highly allergenic substance in view of the rarity with which such a sensitization is found.

One may quite easily assume that contact with various foods is established during intra-uterine life. In such case, however, the state of active sensitization should be evident at birth, but this has never yet been demonstrated in the studies on the cord blood of newborn infants.

In 1909 Gillette[1] pointed out that almost all cases of sudden death from diphtheria antitoxin followed the first injection. By what contact was this sensitization induced? Probably not by horse dander, for from the guinea pig experiments on anaphylaxis there is no proven antigenic relationship between the two antigens, and horse meat is a doubtful sensitizer because of its uncommon use, at least in the United States. This is a point which has never been explained and is merely ignored by those who adhere to the contact theory in the production of the natural or spontaneous clinical allergies in man.

Among the antigens not infrequently encountered in human allergy are such non-protein substances as acetylsalicylate (aspirin), iodides and essential oils, such as wintergreen, peppermint and cashew. Some of my aspirin-sensitive patients have insisted that their first asthmatic reaction followed the first use of the drug. Conceivably such a simple compound might form a combination with body protein, the so-called hapten of Landsteiner,[20] but why then is the percentage of sensitizations so low when the drug is so widely used, and why is asthma caused by aspirin sensitivity seen practically only in cases of infective asthma? This latter fact may offer a clue to the future solution of this interesting problem.

In this connection another point is of interest. The spontaneous allergy to pollen protein resulting in hay fever and those similar sensitizations to animal danders once started persist, often throughout life, even in the absence of continuing contact. An illustrative case which I have frequently cited is that of a patient who after having had ragweed hay fever in boyhood spent sixteen consecutive years in France where ragweed does not exist. On return to this country during the pollen season he promptly had severe hay fever and asthma. Such protracted sensitization is rarely seen in artificially induced protein sensitization such as that following serum disease, which usually is measured by weeks or months.

Occasionally one encounters a patient with asthma beginning in childhood and with a history of an antitoxin (horse serum) injection several years before with no untoward effect. In such circumstances a later horse serum allergy is attributed to the previous contact. I recall a patient in whom the circumstances were those just stated. She was sensitive to horse dander and to horse serum, but the skin reaction to rabbit serum and dander was much more active. From studies on anaphylaxis one could not assume that the diphtheria antitoxin (horse serum) injection produced a more acute sensitization to rabbit than to horse. In the absence of any discoverable contact with rabbits the allergy may be assumed to have developed spontaneously and if to rabbit then undoubtedly also to the horse antigens. These occasional cases show the fallacy of a too hasty conclusion that prior contact is an essential factor in the later sensitization.

(2) HEREDITY. As to a second possible factor in the pathogenesis of human allergy, studies[6, 21] have been made and confirmed showing that a definite familial relationship exists in so far as the spontaneous allergies are concerned. An antecedent history of clinical allergy is found in over 50 per cent of all patients suffering from the common allergic diseases. This hereditary influence is shown in the number of offspring affected and the age when allergy appears. Spain and Cooke[22] showed that nearly 75 per cent of all children with bilateral antecedent allergy would develop allergy, while of those with a unilateral history only about one-half were calculated to become reactive. With family antecedent history negative the percentage dropped to 40 per cent. When allergy exists in both father and mother the age of onset of symptoms is much earlier in the offspring, within the first five years of life in 36 per cent, whereas with unilateral inheritance the maximum incidence of onset is between the tenth and fifteenth year. When antecedent history is negative for allergy the curve of incidence is maximal at about the thirtieth year (see Fig. 1). The fact that paternal hereditary influence is as great as maternal and that clinical allergies are identical in the majority of identical twins further substantiates evidence for inherited factors in certain allergies.

A comparison of the antecedent and descendant allergies shows that the sensitization is just as apt to be different from as identical with that found in the mother or father. In other words, as originally expressed,[6] "Sensitized individuals transmit to their offspring not their own specific sensitization but an unusual capacity for developing bioplastic reactivities which eventuates into some form of clinical allergy." With this much of that earlier concept I can still agree.

Whether the inheritance as was then believed is a strict dominant or one of the more complex types dependent upon autosomal or sex-linked genes is not so clear and for the clinician not too important, but the answer would be of scientific interest and might be significant. But if one is informed on the years of experimental matings needed in such rapidly produced generations as, for example, in poultry, merely to determine some relatively simple character of feathering or color, it can be readily understood that the human race does not lend itself to the precise study necessary to establish many of the facts of heredity in man.

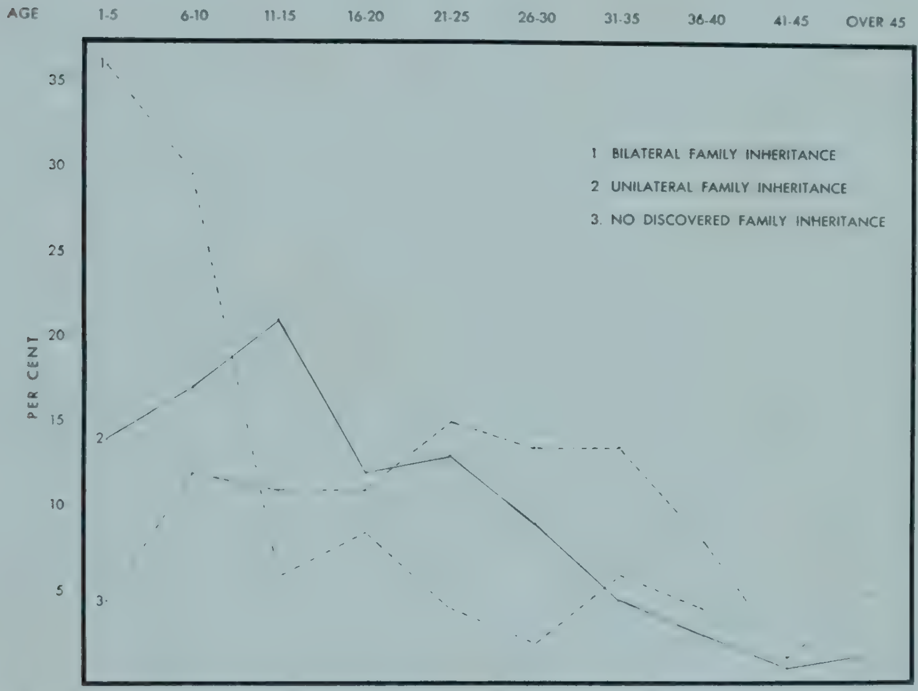

Fig. 1.—Influence of heredity on age of onset of clinical allergy. (Redrawn from data published originally in J. Immunol. *1*:210, 1916.)

After all is said and done the number of known allergens to which sensitization can be purposely induced in any large percentage of the human race (the physiologic allergies) is really very small. Even after prolonged exposure in likely industries Schwartz and Tulipan[23] give the incidence of contact dermatoses as only 1.2 per cent. Even with the present extensive use of sulfonamides the number of persons sensitized is only about 2 per cent, if the crystallization of the drug in the kidney is excluded as a mechanical effect, although some cases do give evidence of an allergic or toxic renal action. This percentage is not higher in those with clinical allergy, a group that might be considered predisposed. The idea of Dowling and Lepper[24] in this regard seems entirely justified, namely, "It is possible that patients who are going to develop drug fever will do so during the first or second course or not at all," and this seems to be the general trend of medical opinion today.

These facts indicate that even with adequate contact the constitutional make-up which is heredity is the important factor in all sensitizations, including those induced by known contacts, and this is so in spite of the fact that certain substances are much more active sensitizers than others. What these constitutional factors are cannot even be surmised, for they are not obvious as they are in the spontaneous familial allergies.

(3) INFECTION. A clinical history of an acute infection, especially pertussis, measles, pneumonia, influenza or bronchitis, as the precursor of an allergy, is obtained too frequently to be overlooked or regarded as of no moment. More unusual is the case of milk allergy following an acute enteritis, as reported by Schloss and Worthen.[25] Further substantiation for the theory that infections may be factors in the pathogenesis of allergy is afforded by Bailey's[26] findings of hemolysins in the serum of rabbits after infection with *Bacillus lepisepticus*, and by Burky's[27] work showing the enhancing synergistic effect of staphylococcus toxin on feeble antigens. Infection as provocative of an allergy but not specifically and causally related to that allergy is an idea that must be investigated further.

SUMMARY. The facts appear to warrant the conclusion that there are certain allergies, examples of which are cited, which definitely are developed as a result of contact with an antigen, they are producible at will in the majority of human beings and for that reason have been termed "physiologic" or "normal" allergies.

In striking contrast is the group in which development of clinical sensitization is spontaneous and results in the recognized diseases of allergy. They arise from no special or purposeful contact with an antigen, if there has been any contact at all, and in them hereditary factors play a definite part. This group affects but a small proportion, probably less than 10 per cent, of the population and, as a rule, sensitizations are carried through the major part of life. This group I have designated as "spontaneous" allergy.

One can never assert that contact has not occurred at some previous time for this is not possible to prove. Neither can it be asserted that through inheritance a person has been rendered a ready victim to any or all sensitizations. Cooke and Vander Veer[6] showed that allergic patients who had had previous antitoxin injections, some with serum disease, did not remain skin-reactive to horse serum longer than nonallergic patients.

All that can be said now is that if contact is necessary, a very slight one may suffice to set off a variable and self-perpetuating mechanism of reaction to an allergen that is predetermined by nature or inheritance, while other contacts great and small are ineffective in the development of the clinical allergies. Why one should become sensitive to horse serum with which there is no known contact instead of to milk which is taken in large amounts cannot be answered. The concept of contact stimulation alone is far too simple for it does not explain the vagaries of the sensitizations of man, the part that heredity plays or the allergies to non-protein drugs. The complete answer remains in the future.

X-Substances of Antigen-Antibody Reactions. No one yet knows why tuberculin produces its typical reaction in a person or animal sensitized with viable or dead tubercle bacilli. Primarily, in the nonsensitive individual tuberculin is inert, while in the presence of specifically sensitized cells it produces an inflammatory reaction. The same ignorance shrouds our knowledge of why the oil of ivy produces a vesicular dermatitis in sensitized cells of the skin but does nothing in the absence of sensitization. For the present, however, it must be assumed either that some toxic agent is liberated, different for the different types of allergic response, each to produce its own special effect, or that the specific antibody permits the antigen to exert its own effect upon the sensitized cell. I have used the term X-substances in order to include these unknown theoretical "*allergo-toxins*" as they may be called, along with histamine (H-substance) now to be considered. The supposition holds for all types of reaction which are assumed to be allergies and in which the mechanism of reaction has not been proven but which is predicated today upon hypothetical cellular antibodies. These are the riddles for the future students of allergy to solve.

HISTAMINE (H-SUBSTANCE). The type of allergy about which something is known is that in which the patient gives a prompt wheal on skin test with the allergen responsible for the clinical allergy, for example the ragweed pollen which produces autumnal hay fever. It is significant that, regardless of the chemical and biologic nature or source of the antigen, the expression of the reaction is essentially the same in this particular type of allergy. In other words, the person who has the immediate wheal type of allergy gives the same response of hyperemia and edema whether the allergy be to egg or to animal dander, although the clinical expression may vary with the degree and especially with the area of tissue sensitivity or what has been called the shock organ.

It was this fact, so evident in the early work on anaphylaxis, that led to the conclusion that there was a single substance, a so-called anaphylatoxin, produced by the union of an antigen with sensitized cells in this type of protein sensitization. The same hypothesis was then applied to the allied reactions in the naturally sensitive man. From a purely theoretical point of view this idea has great plausibility and appeal if it is limited to that particular type of allergy which is associated with the immediate skin reaction and those clinical manifestations resulting from reactions which produce edema and hyperemia. It does not appear to me that this same explanation can be made to apply to the delayed allergic reactions of the tuberculin type and those resulting in exudative dermatoses as eczema and dermatitis venenata, although many workers are trying to include such allergies together with the immediate wheal-reacting group. In this discussion all such will be excluded.

In the Herter Lectures of 1919, Dale[28] reviewed the studies by himself and his associates which led to the conclusion that histamine was the long sought anaphylatoxin that had been hypothesized from the beginning of the work on anaphylaxis. Because of its presence in normal tissue and on account of its potency and pharmacologic action "the suggestion," as Dale says, "lay near at hand that the long sought active substance was histamine and that the production of the latter in the system was the cause of the anaphylactic shock." With the introduction of a method for quantitative analysis, studies on histamine in anaphylaxis and human allergy began in earnest. It should be pointed out here, however, that the methods of Barsoun and Gaddum[29] and of Code[30] are biological assays using smooth muscle as the indicator. They are not estimations of histamine itself and therefore are subject to the inadequacies of all such assays, for substances other than histamine stimulate smooth muscle contraction and all such analyses are suggestive rather than conclusive.

It is not necessary to review in detail the very extensive literature for that has been done adequately by Feldberg[31] and by Dragstedt.[32] This discussion will deal only with histamine in its relation to experimental anaphylaxis and to human allergy of the wheal reacting type, for this latter is the type of allergy in which histamine would most likely be a factor if one at all. But if it should be shown that histamine is the toxic factor in the immediate wheal type of allergy it does not follow that it plays any part in those allergies which have a different immunologic basis, such as tuberculin allergy and the allergic dermatoses.

IN ANAPHYLAXIS. In animal anaphylaxis the general trend of opinion is definitely in favor of the view that histamine is liberated in amounts sufficient to account for some of the shock symptoms, while other anaphylatoxins such as heparin and perhaps acetylcholine have other effects determined by their own pharmacologic activities. As Feldberg[31] puts it in the review mentioned, "We have further to realize that the histamine theory does not pretend and never pretended to reduce all the manifestations of the antigen-antibody reaction to histamine effects."

Most of the experimental work, however, has centered about histamine but a few workers have given attention to the possibilities of other and perhaps more important factors. Recently there has been an interesting contribution by Campbell and Nicoll.[33] They showed in a very neat experiment that rat uteri "unaffected by ordinary doses of histamine respond in the tissue bath to some substance released by sensitized guinea pig lung tissue during anaphylactic shock." They have not attempted its identification. It may have been a cholinergic substance, or possibly peptone, or it may have been the muscle-stimulating compound similar to that which results from the action of venoms on living tissue or on lecithin. At any rate it seems that in this particular experiment some substance other than histamine must have been liberated in the antigen-antibody reaction.

That histamine is not the complete answer was also suggested in a simple experiment carried out in my laboratory.[34] A similar experiment had been done earlier by Schild.[35] The uterine horn of a guinea pig sensitized to ragweed pollen protein was suspended in the tissue bath and was repeatedly shocked by the addition of histamine until it ceased to respond, histamine remaining in the bath. When completely relaxed, the ragweed antigen was added and a prompt contraction of the uterine horn ensued. The results were the same with atropinized muscle, hence acetylcholine was not the factor. Our conclusion from this experiment was in accord with that of Schild,[35] namely, "that either histamine released from the cell had a different action from that of histamine applied to the cell surface or it plays only a secondary part in anaphylactic shock."

Lewis[36] appears to suggest in some of his studies on the "triple response" that all capillary permeability in tissue injury is due to a chemical H-substance which presumably is histamine. Menkin,[37] however, in studies on inflammation, has obtained results which "indicate that the active factor recovered from an inflammatory exudate which is capable of inducing increased capillary filtration primarily by injury to the endothelial wall, does not seem to be histamine nor is it the H-substance in so far as its properties are supposed to resemble closely those of histamine." Menkin finally isolated and crystallized this substance which he called leucotaxine.

From another angle, then, histamine has been deprived of its importance as the sole agent in the causation of capillary permeability, which is one of its attributes in anaphylaxis. While it is a substance existing preformed in the tissues and powerfully toxic when liberated from its bound state in the cells, it would appear not to be the sole factor in anaphylactic shock but probably is an important one of several.

Recently, however, Fell et al.[38] brought forth some new evidence suggesting the importance of histamine in anaphylaxis. The non-antigenic histamine molecule was bound to a despeciated horse serum globulin. Injection of the conjugate into guinea pigs produced precipitins in their serum which were interpreted as being specific for the hapten portion (histamine) of the antigen. Further, such animals were found to be refractory to histamine by injection, and when previously sensitized actively or passively to crystalline egg albumin they were relatively refractory to anaphylactic shock in comparison with the control group This to the present is perhaps the most significant work supporting the thesis that histamine is the dominant cause of the explosive reaction in anaphylactic shock, at least in the guinea pig. This work has not yet been confirmed and results may be susceptible to an explanation other than that which now seems obvious.

IN HUMAN ALLERGY. Current literature on this subject is extensive, confusing and often contradictory. Based upon the studies on anaphylaxis, and because it produces an allergic type of wheal in the skin, histamine is accepted by many as the agent responsible for the symptoms, not only in allergies of the usual wheal-reacting type such as asthma, hay fever and urticaria, but also as the active agent in a varied group of clinical conditions as traumatic shock, eczema, certain types of headache, Ménière's disease and urticaria due to physical agents, especially to cold. The studies that have been made range from determinations of histamine in allergic reactions to observations on therapeutic effects of the administration of histamine in various forms.

Assays of histamine in the blood might well be disregarded, for judging by the definite systemic effects of such a dose as 0.1 to 0.2 mg. of the base, which does not elevate the blood level, a severe reaction might be due to histamine liberated in the tissues but still not be determinable as an excess in the blood. On the other hand histamine has been found by Barsoum et al.[39] to be in excess in the human blood after burns without producing any anaphylactic or allergic effects, but since this excess histamine is probably intracellular and therefore devoid of pharmacologic effect the observation is not highly important.

There are other observations more likely to be of significance. It has been stated that if a wheal appears in a certain skin area it does not reappear in this area for thirty-six to forty-eight hours, that is, the skin is temporarily unresponsive due to failure of the cells to form H-substance. Alexander[40] recorded such an observation in a patient with cold allergy. I have repeated this experiment in several such patients and the reapplication of ice to the exact wheal site after twenty-four hours resulted in a more active wheal than the one primarily obtained. The same result was obtained by the immersion of the hands in ice water. Unresponsiveness could not be demonstrated.

Histamine by injection has been widely used on the assumption that one could thereby relieve allergic wheal type reactions either by the stimulation of excess histaminase, or through the saturation of the cell receptors for histamine (histamine desensitization) or by the development of histamine tolerance, a sort of immunity. There are many clinical reports in the literature. At first, as is often the case, they were highly favorable, recently they have been less so. In my clinic therapeutic effects in urticaria and in cases of chronic asthma were nil.

It is stated by Cohen and Friedman[41] that "it is true that individual constitutional tolerance to histamine can be increased many fold following its parenteral administration. . . ." I have never been able to secure any appreciable increase in the tolerance to histamine.[47] Even after months of treatment with histamine in normal or allergic patients the amount that would produce slight objective reactions remained unchanged. It is true that such injections never change the level of the intracutaneous response. Both normal controls and allergic patients are equally reactive to histamine by any method of injection.

HISTAMINASE. Other attempts have been made to support the histamine thesis by the use of histaminase. This enzyme is a normal constituent of certain body cells, especially those of the kidney and intestinal mucosa. On account of its histamine-destroying effects it has been used to prevent the anaphylactic reaction. As was to be expected, it was then used promptly as a therapeutic agent in the clinical allergies of man. The first reports of its use to prevent anaphylaxis were gratifying (Karady and Browne[42]) but later results were negative (Alexander and Bottom[43]). Extended clinical trial has likewise resulted in contradictory reports as collected by Farmer.[44] In general, observers after more prolonged experience have failed to show any benefits in this form of treatment and I have found it devoid of any therapeutic effect in any type of allergy.

The reasons can be briefly summarized: Taken by mouth the enzyme is destroyed by the peptic and tryptic digestion. There is no evidence that the enteric coating on the tablets now commercially available can protect histaminase from the effect of intestinal enzymes. The action of the enzyme in experiments in vitro is so slow that it could never be effective in the body in neutralizing the theoretically liberated histamine which is responsible for such rapid explosive reactions as those occurring in the wheal-reacting type of allergy and in anaphylactic shock of the guinea pig. As marketed, the preparation has been found frequently to be inert when tested in the laboratory for its histamine-destroying action.

The beneficial effects of histaminase in human allergy are based entirely upon the patients' reports and the objective findings. Allergic manifestations are noted for their variability of course and intensity.

so that reports based upon such observations are highly unsatisfactory. Only when one can reproduce an allergy at will and prevent its appearance regularly by the use of this enzyme is it possible to speak with any degree of assurance. The literature does not reveal any reports of such carefully controlled but properly expected experiments. In my opinion the continued exploitation of this drug is unwarranted.

HISTAMINE-AZO-PROTEIN. Clinical studies using the histamine-azo-protein of Fell have been reported by Sheldon et al.[45] after several years' trial, with results which they say are "sufficiently encouraging to justify a continuation of the study." Cohen and Friedman[46] have used this product, now sold under the trade name of Hapamine, but their work is still in the experimental study stage. Their recent paper[41] concludes with the statement that "since both the eserine wheal and the allergic wheal are mediated by an H-substance mechanism, we see no reason to doubt that there would also be protection against the H-substance released in an allergic reaction." However, this positive statement with regard to the eserine wheal is based entirely upon the work of Alexander[40] which, as the previous authors state, "has demonstrated that the wheal produced by eserine resembles in all respects that which occurs in allergic reactions," but resemblance is not proof of identity. Although Cohen and Friedman[41] claim that the histamine threshold is materially and significantly elevated after Hapamine therapy, they present no evidence in this paper that a histamine antibody was present in the serum to account for this effect.

I have not been able to verify these findings. Actually there is as yet no convincing and confirmed proof that H-substance is liberated in the allergic wheal. In spite of the fact that histamine-azo-protein (Hapamine) has been used for over three years there are still no published reports that it exerts a beneficial therapeutic effect in any single allergic disease, except by inference.

A recently completed work by Hebald, Cooke and Downing[47] showed that Hapamine injections did not protect cases of pollen hay fever, did not prevent constitutional reactions in ragweed-sensitive patients who had a fixed level of ragweed extract dosage, and did not alter the level of cutaneous reaction on intradermal test to the histamine base. In no case, regardless of the amount or duration of Hapamine therapy, was a precipitin specific for histamine present in the serum.

The commercial product is not to be used carelessly. Mills[48] has reported systemic histamine effects and I have not infrequently noted severe local and systemic reactions after injections. This contribution of Fell's[38] which for a time seemed to offer such interesting possibilities in human allergies has seemingly failed to live up to its expectations, and the continued marketing of the product for therapeutic purposes is not justified.

Specific Causes. Antigens or allergens must be absorbed to produce clinical effects. For convenience they are often classified according to the usual or conventional method through which contact is established, that is, they are inhaled, ingested, injected, absorbed from areas of infection or from external contact. This so-called classification is generally useful and correct.

INHALED SUBSTANCES are air-borne and include the pollens, mold spores, animal danders and feathers, and such various organic dusts as the unknown factor in house dust, the fabric dusts of cotton and kapok, as well as toilet articles, face powders and hair set lotions and the flour of various grains as wheat, corn, and rye. Inhaled substances, as should be expected, exert their allergic response in the membranes of the respiratory tract, hence they are common causes of allergic coryza and asthma. When inhaled, air-borne substances do not produce the allergic dermatoses or urticaria and angioedema of the skin, intestinal tract or cerebrum except in the very exceptional case. However, certain substances that are air-borne may act as external contactants. For instance, pollen is known to produce a seasonal dermatitis, though this is rare.

INGESTED SUBSTANCES comprise both foods and drugs. Any food may be a cause of an allergic reaction. Eggs, milk and wheat are generally considered as the most frequent and important. Banana, strawberry, cantaloupe, chocolate, celery, potato, tomato, liver, fish and shellfish are not rare causes of allergy.

Any organic drug and a few that are inorganic may act as allergens, but the common ones are acetylsalicylic acid (aspirin), quinine, opium derivatives, sulfonamides, ipecac, senna, iodine, arsenic and thiamine.

The ingested foods and drugs in the sensitized person, depending upon the locale of the reacting tissue and the immunologic type of sensitization, may produce the following allergic manifestations: coryza, asthma, urticaria, angioedema, any gastro-intestinal symptom simulating gastroenteritis and acute and chronic colitis or the evidences of an acute abdominal condition, cerebral allergies, dermatoses and purpura. In fact any and all known allergic diseases may be caused by ingested substances.

There is still a great diversity of opinion among practitioners of allergy concerning the relative frequency of food allergies. One school places great emphasis upon them, the other, to which I belong, believes that while they are highly important in the individual case they are relatively uncommon in adults and in children after the sixth year. The methods of diagnosis are important and will be discussed.

INFECTION. The absorption of bacterial substance or the products of their growth from areas of acute infection or from a chronic focus may produce any type of allergic disease. Bacterial allergy is a common cause of vasomotor rhinitis, hyperplastic rhinitis and sinusitis, asthma acute or chronic, erythema multiforme, lupus erythematosus, the dermatoses including "infantile eczema," urticaria and angioedema, both dermal and gastro-intestinal, the allergic encephalopathies and the vascular lesions of periarteritis nodosa. The organisms usually recognized in these cases are the streptococcus, staphylococcus and the pneumococcus of all types. Other bacteria and viruses may be causes but are less frequent. Infection as a cause of allergic disease is not yet as well recognized as it should be. The difficulties of diagnosis and of establishing proof are probable reasons in addition to the fact that as yet little or nothing is known of the mechanism of the reaction.

INJECTED SUBSTANCES. These comprise all drugs and therapeutic serums administered by subcutaneous or intravenous route. While relatively uncommon, allergies to all such are highly important because of the serious and frequently fatal results. The reactions are usually prompt with erythema, edema, dyspnea, with death from asphyxia or cardiac failure. All foreign protein such as antiserums and liver extract should be given only after appropriate test, especially to those known to have any clinical allergy. Most drugs such as quinine and iodides should be given first by mouth. Diodrast should be used only with the greatest caution in known allergic persons. In my opinion it ought not to be injected unless absolutely essential to a diagnosis.

EXTERNAL CONTACTANTS. As with inhalants the allergic lesion appears at the point of contact. It is a dermatosis with rare exceptions. If absorbed in sufficient amount the skin lesion may appear elsewhere than at the point of contact. Very rarely a drug externally applied may produce other allergies such as asthma, but only after sufficient absorption. I recall the case of a woman who developed first itching and erythema of the hands and arms and then severe asthma after applying tincture of delphinium to her daughter's hair. There was no dermatosis. At the clinic a cork moistened with the drug was touched to the unbroken skin of her forearm. In less than five minutes there was local widespread erythema with a typical lymphangitis running up the arm to the axilla. Immediately the patient developed a cough, dyspnea and a typical hay fever attack which responded quickly to an injection of epinephrine. It is not necessary here to discuss in detail the important contactants which produce the allergic dermatoses. (See Chapters 13, 14, 15.)

In general then, in undertaking the study of an allergy or a probable allergic manifestation for an etiologic diagnosis, one must think in broad terms of the groups of causes and ask himself the question "Is this due to inhaled or air-borne substances, or is it due to foods or drugs; is there a discoverable focus of infection, or may external contact allergens be the answer?" The points already given, together with the discussion under diagnosis (p. 34), should be kept in mind.

Non-specific Causes or Influences: These are discussed in various individual chapters. A more detailed discussion of them in relation to allergic disease is to be found in the Appendix.

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2. *Principles and Theory—Continued*

ROBERT A. COOKE

Clinical Immunology

CLINICAL observation indicates two immunologic types of allergy depending upon whether the reaction occurs *immediately*, that is within an hour after contact with an antigen, or is *delayed* beyond that time.

Immediate Reaction. When a patient with asthma gives a history that contact with horses is followed promptly by nasal and chest symptoms of coryza and asthma, then a skin test with a horse dander extract will give a typical wheal within a few minutes. A drop of the extract in the eye is likewise promptly followed by itching, tearing and redness. This is so with only the rarest exceptions. Conversely, whenever extracts of danders, pollens, dusts or foods give an immediate skin test reaction then proper contact with that substance will provoke a prompt clinical response *if any at all results.* An accurate history of clinical reactions following immediately (a few minutes to one hour) upon contact with an allergen whether inhaled or ingested will, in general, be substantiated by an immediate wheal reaction on skin test with an extract of that substance. The serum of such persons contains the skin-sensitizing antibody which may be transferred to normal skin. It is in this type of allergy and in this type alone that skin tests are useful provided they are properly interpreted and assessed as to their clinical significance. This *immediate* reaction occurs only in the patient with an existing sensitization and should not be confused as it sometimes is with the "immediate" reaction described by von Pirquet[1] and which he defines as "within twenty-four hours" in children after reinjections of serum. This latter is really an unusually accelerated response of body cells prepared by a previous serum injection for a quick reproduction of the anaphylactic antibodies. It is not a reaction with a pre-existing antibody induced by previous injections of serum (anaphylactic shock) or naturally found in the serum-sensitive asthmatic man.

I have stated the general rule that an immediate skin reaction indicates an immediate clinical reaction and vice versa. But there are exceptions. An immediate skin test reaction does not necessarily indicate clinical sensitiveness. The reason for this is not yet entirely clear. There are at least two conditions which may exist that seem to afford an adequate explanation and there may be others. One is the existence of an apparent protective immunity as will be discussed later (p. 64, Patient JOH). The other is the fact that sensitization does not exist in the tissues with which allergen contact naturally takes place. Hence a reaction and clinical symptoms do not occur. The case of REB affords an example; this patient had typical autumnal hay fever with reactions to ragweed extract. The skin reacted to timothy extract somewhat more actively, but there were no symptoms of coryza in the timothy pollen season. The eye test with a strong extract of timothy was negative for timothy, whereas there was a positive eye test reaction with ragweed extract. In other words there was no mucous membrane sensitization to timothy. This is not uncommon. These positive skin tests that have no apparent clinical significance are frequently spoken of as "false" positives. A skin test with a proper extract that regularly or repeatedly gives a genuine pseudopod wheal reaction, and such frequently occur, is not in my opinion correctly termed "false" just because there is no clinical evidence of a sensitization. The serum of such patients will transfer the reaction, and there is at least a skin sensitization, for if a sufficient amount of allergen is given subcutaneously or intravenously (a dangerous procedure) a general urticaria may result. The tests do not lie. They are positive and genuine but "asymptomatic" rather than "false." The absence of typical or expected symptoms as in the case of the pollen reaction cited above may be due to the absence of sensitization in the usual shock organ, or it may be due to the fact that certain "extra-specific" reactions are caused by antigens, related or subsidiary to the dominant antigen. (This is discussed on page 49.) Our knowledge is not sufficient to explain all these results.

The situation is different in the case of the tests that give only "slight" or "moderate" reactions which vary on repeated testing and are not transferable, and may be due to improper extracts or vascular response in so-called irritable skins. These really are not positive tests and should not be so interpreted.

Further, in certain allergic patients the ingestion of even small doses of acetylsalicylic acid (aspirin) produces in twenty minutes or less an attack of severe dyspnea of the asthmatic type which may progress, as in a few recorded instances, to a fatal termination. Urticaria is not a part of the clinical picture in these cases and a skin test with the antigen has been uniformly negative. Such tests are dangerous and should not be done routinely. I have seen a sharp asthmatic reaction induced by an intradermal injection of 0.0001 mg. of the drug. Non-protein drugs may give immediate allergic reactions as asthma but the skin test is negative in all cases in which an immediate urticaria is not a part of the clinical picture.

With protein substances, however, an immediate clinical reaction is, with reservations as stated above, indicated by an immediate wheal reaction. Among all my records there is but one well confirmed example of an immediate asthmatic reaction to protein, in this case to fish, with no corresponding immediate wheal reaction. In short, immediate clinical and skin test reactions go hand in hand. Whatever the substance liberated or generated in the immediate reaction may be, it acts at once or not at all and it can only produce the erythema-edema type of response and no other. In other words, it cannot produce the lesions of dermatitis, purpura or other delayed inflammatory manifestations.

Delayed Reaction. In contrast with these immediate reactions are those in which the allergic symptoms appear several hours to several days after contact with the allergen. These I have designated as *delayed* reactions. They are not an immunologic entity for it is probable that there are several different mechanisms involved.

Inflammatory. Mention has been made of the allergic dermatoses including eczema, the bacterial allergies, and certain types of purpura—in general, the inflammatory reactions. All of these are delayed and the proof lies in the obviously delayed local response that may be induced at will by contact with known antigens such as oil of ivy or tuberculin, and in the evidence of a late clinical reaction such as purpura which may be reproduced in the relatively rare patient with purpura when the offending food or drug has been discovered and is used again.For example, there is the patient previously mentioned (p. 8) who had hematuria due to purpura of the bladder mucosa which appeared six to eight hours after taking 5 grains of potassium iodide.

Of all these late reactions nothing of basic significance is known except their existence. There is no knowledge as to how or why they occur or are produced. Actually it is purely an assumption, except in the case of the tuberculin antibody, that there is a specific antibody in the reacting cell, but it is a reasonable and stimulating hypothesis in view of Chase's[2] demonstration of a cellular antibody in tuberculin allergy.

Edematous. In addition to the inflammatory responses, and based on a still different immunologic mechanism, there are the well substantiated cases of delayed edema reactions to foods such as milk, chocolate and fish, and to certain drugs. Air-borne substances very rarely produce this type of late response. Clinical evidences of such reactions may be urticaria, angioedema manifested by cutaneous, cerebral or gastro-intestinal symptoms, less often asthma and coryza, in other words functional edema reactions. The direct and passive transfer skin tests are negative when the apparent allergen is used in the test. At present these cases can be diagnosed only by observation and clinical tests. The interesting features are that the reaction always follows sufficient contact and always has a definite incubation time. Frequent recurrences of the clinical reaction fail to modify, to shorten or lengthen this time interval. These delayed clinical reactions are therefore not in any way related to serum disease with its varying period of incubation, for after serum disease the skin test is positive and immediate.

A typical example of delayed reaction was seen in a woman with chronic urticaria of many months' standing. Symptoms ceased when chocolate was withdrawn from her diet. When fed chocolate in fixed quantity urticaria always returned in approximately twenty-six hours on repeated trials. The skin test with chocolate was negative.

Seemingly this is a different mechanism of reaction from that existing in the *immediate* type, but this difference is more apparent than real. Some years ago I described such cases[3] and later[4] advanced the theory that perhaps these delayed reactions were immunologically identical with the immediate reactions; that the real allergen in the delayed reactions might be a product of protein cleavage which took time to elaborate within the body from the foods or drugs that were the apparent cause as determined by the clinical test.

While conducting some studies on allergy to tetanus toxoid,[5] it was discovered that, contrary to current opinion, proteoses were antigenic. Further studies[6] on protein derivatives (proteoses) of milk, egg and chocolate disclosed some cases that were found to be sensitive to such split products by an immediate skin reaction which was transferable. C. Z., a man aged thirty years, had a history of continuous asthma of several years' duration and frequent exacerbations occasionally complicated with acute gastro-intestinal attacks. Pollens and molds were responsible allergens confirmed by immediate wheal reactions and clinical history. Skin tests to foods, including milk, were negative and there was no definite history of food allergy but the patient was suspicious of milk. Tests with the *primary proteoses* of whey of cow's milk were positive by the direct and indirect method. Under hospital observation, the patient two hours after ingestion of a quart of milk had nausea, asthma, abdominal pain and several loose stools. Two other trials produced identical results. The two-hour incubation period was definitely fixed.

This would appear to confirm the suggestion that in this particular form of *delayed* reaction the delay is more apparent than real and is merely the period of digestion and of preparation of the real antigen from the food substance which regularly causes the clinical response. The immunologic basis, then, is really identical with the so-called immediate reaction. Spain,[7] among others, has confirmed these observations, but such reactions are still classed as delayed on a clinical not an immunologic basis.

Multiple Sensitivity. One of the intriguing facts about the allergic patient is the great frequency with which more than one clinical allergy is found in the past history or as a coexisting condition. Swineford and Weaver[8] in a series of 200 patients gave 88 per cent as the frequency "with which several allergic conditions occur in the same individual."

In a study of hay fever in 1916 Cooke and Vander Veer[9] found that 30 per cent of 530 patients were clinically sensitive to grass and ragweed pollen. At least another 10 per cent could be added to this if the various tree pollen cases were included. Here is an allergy (hay fever) that is clinically a single entity but in reality is a multiple sensitization, as the pollens of trees, grasses and ragweeds are different allergens. In certain instances one finds a past history of allergic dermatitis (infantile eczema) in a child with asthma or one finds a patient with coexisting dermatitis and asthma, each due to an unrelated and separate allergen. In other instances a patient with asthma of infective origin is sensitive to aspirin which also produces asthma.

The question of multiple sensitivity should not be answered on the basis of positive skin tests alone for there are many positive tests that are not indicative of a cause of allergic reactions, nor should it be viewed on the basis of the clinical syndrome alone. Multiple sensitivity means that the patient with one or more definite clinical manifestations is susceptible to clinical reactions to more than one unrelated allergen. It is not likely that the 88 per cent of Swineford and Weaver[8] is too high if clear-cut past allergies are included. In other words, if a man has hay fever from trees, grasses and ragweed, he has multiple sensitivity, though only one clinical manifestation, just as much as the patient who has asthma and allergic dermatitis.

Serologic Immunology

As to the mechanism of reaction for such delayed allergies as those resulting from tuberculin and oil of ivy there is little information. However, in the immediate allergies immunologic studies have yielded some results, though information is limited and conflicting both as to fact and interpretation.

A Comparative Study of Anaphylaxis, Serum Disease and Asthma. These three conditions form an interesting trio for comparison when horse serum as the antigen is the assumed common denominator. It is not indicated here to make a complete review of the literature as this has been ably done recently by Longcope,[10] nor shall I review in detail the subject of experimental anaphylaxis which is adequately covered in many treatises and is aside from the point and scope of this book. Certain significant facts will be discussed only in so far as they apply to the problem of the clinical allergies of man.

In *anaphylaxis* it is well known that in the guinea pig the state of sensitization develops in eight to ten days after parenteral injection of protein and that in this animal it is very specific, as Dale and Hartley[11] showed. Different antigens vary in their capacity to sensitize, depending upon the nature of the protein and the route and method of its administration. Desensitization, as well as the passive transfer of sensitization, is readily accomplished in the experimental animal. Reversed anaphylaxis, first described by Opie,[12] is an interesting phenomenon.

What is not so well appreciated is the nature of the several antibodies produced in the anaphylactic animal. By different immunologic technics, precipitins, muscle-sensitizing antibodies and skin-sensitizing antibodies have been found. The precipitin and smooth muscle-sensitizing antibodies are readily demonstrated, the former in vitro and the latter by the Schultz-Dale experiment. The transfer of a skin-sensitizing antibody from sensitized rabbits' and guinea pigs' serums to the skin of normal man (Prausnitz-Küstner phenomenon) was first demonstrated by Cooke and Spain.[13] We postulated that the precipitating, muscle- and skin-sensitizing antibodies were three different reaction bodies because there was no quantitative relationship between them in a particular serum. This work has been confirmed by de Besche[14] and more recently by Sherman et al.[15] The fact that the skin-sensitizing antibodies are found so rarely, so irregularly and in such low titre in guinea pigs and rabbits explains the absence of conspicuous skin eruptions (urticaria) in animal anaphylaxis as compared with the serum disease of man and the serum reactions in asthmatic man.

Serum disease in man follows the parenteral injection of a sufficient amount of foreign serum. It appears after an incubation period of about eight or ten days. Urticaria is the prominent manifestation of the disease. This symptom is due to the reaction of the developed and cellularly fixed skin-sensitizing antibodies with the foreign serum remaining in the body. With the production of precipitating antibodies in quantity the foreign serum disappears, as Longcope and Rackemann[16] showed, and consequently urticaria disappears, In other words, urticaria is but an incident in the developing sensitization of man. After serum disease the state of sensitization which exists in man is entirely analogous to that of the sensitized animal. Precipitating, skin-sensitizing and smooth muscle-sensitizing antibodies are all present though in varying proportions, as Cooke and Spain[13] showed, in the artificially sensitized man just as in the anaphylactic guinea pig. Passive transfer of skin sensitization is possible from man to man although anaphylactic shock has for obvious reasons not been attempted. Further, it has been shown that the smooth muscle antibody is transferable from man to guinea pig by the technic of anaphylactic shock or uterine horn contraction.

Fundamental differences between the anaphylactic animal and man after serum disease do not appear to exist though there are some distinctions of a quantitative, not qualitative, nature. The most obvious is that serum disease of man is not duplicated in animals, though there are minor evidences of skin irritation in animals in the early stages of anaphylactic shock, and the reason for this is that, as stated before, the animal lacks the unusual capacity of man to produce the skin-reacting antibodies in large amounts. The skin-sensitizing antibodies of man, however, do not appear to have a very high degree of specificity as shown by the experiments in reversed anaphylaxis of Voss[17] and the direct skin tests of Mackenzie.[18] In the sensitized animal the specificity of the skin-sensitizing antibodies has not been investigated because of a previous lack of appreciation of their existence and because a study would be difficult on account of their low titre. There is one other important distinction that may amount to a fundamental difference and that is in the matter of desensitization. In the experimental animal this seems to be readily and completely accomplished, but clinical observations do not indicate that this is so for man. This is well brought out by Tuft[19] in his report of a fatal result following an attempt to desensitize with serum. Similar experiences are reported by Koch[20] and by Blankenhorn.[21]

The difficulty with the interpretation of such clinical studies in man as recorded is the usual incompleteness of the preliminary immunologic study. In Tuft's case,[19] skin, eye and serologic tests had not been done. Other factors that hinder analysis are the species differences of serums and immune serums used therapeutically and the route and amount of the injection. These are defects inherent in the nature of clinical work, but greater care and forethought in the future might help to throw light on some of the remaining problems.

In the spontaneously allergic asthmatic patient sensitive to horse serum, no precipitins and no muscle-sensitizing antibody have as yet been demonstrated, but the existence of a skin-sensitizing antibody is shown by direct test and by passive transfer to normal test subjects and to the Macaca rhesus monkey as demonstrated by Straus.[22] These serum-reacting patients have had no previous injection of horse serum yet one finds the skin-sensitizing antibodies in their serum markedly in excess of those artificially produced by injections of large amounts of horse serum. They persist practically through life even in the absence of immunologic stimulation while in man artificially sensitized to serum the allergic state is as a rule a relatively temporary phenomenon, although Mackenzie[23] has reported sensitization lasting two to eight years. These spontaneously allergic patients can be but partially and slightly desensitized, as shown by Larsen et al.[24]

From an immunologic standpoint then, the identity between the naturally sensitive man on the one hand and the artificially sensitized man or experimental animal on the other is based on the demonstrable skin-sensitizing antibody, and upon this point alone rests the claim that the anaphylactic state of man or animal on the one hand and spontaneous allergy on the other are one and the same.

While not a strictly immunologic point this comparative study might be carried a bit further. It is accepted as proven that the anaphylactic guinea pig dies primarily from asphyxia, due to contraction of the smooth muscle of the bronchi and bronchioles. While there are slight evidences of skin and nasal irritation in the guinea pig, due probably to the skin-sensitizing antibodies which may be present, tissue edema is not characteristic and has never been described as occurring in the bronchi and bronchioles even though an autopsy is done immediately after the fatal shock. To anyone who has observed the severe immediate systemic reaction in man, edema of the skin and mucous membrane is the outstanding manifestation and by the same token edema of the mucosa in the bronchi and bronchioles is a more logical explanation for the respiratory obstruction causing asthma, often fatal, in the naturally serum-sensitive asthmatic man. This is not confirmed by the autopsy reports but in man the examinations are delayed and conceivably it is not looked for carefully in these rare autopsies.

Another point is that in the asthmatic man there is no immunologic mechanism for bronchial contraction as the smooth muscle-sensitizing antibody has not been demonstrated. If it were present in these cases it should be transferable to the guinea pig as is done so easily with the serum of man after serum disease. In fact there is reason to question the existence of bronchospasm rather than edema in the production of dyspnea in the spontaneously developed allergy (asthma) of the immediate wheal-reacting type. Most of the pathologic data on bronchial muscle hypertrophy resulting from bronchospasm have been obtained on chronic asthmatic patients with chronic bronchial infection and are not necessarily applicable in the type of acute asthma under discussion.

Whether sufficient histamine could be liberated to produce its pharmacologic effect on the smooth muscle of the bronchi is a theoretical possibility that has not been proven, but it is not liberated in the smooth muscle cell for as stated there is no demonstrable muscle-sensitizing antibody.

A clinical observation which I made many years ago (before anaphylaxis and allergy were appreciated) is pertinent here as it bears upon the relationship of serum disease to the spontaneous allergy to serum in man. The patient was known to have asthma from contact with horses and other animals. A protective dose of diphtheria antitoxin was injected. There was an immediate and almost fatal reaction. Asthma with urticaria and edema as the dominant symptoms completely subsided by the third day. On the ninth day after the shocking dose a typical serum disease began and ran a moderate course of four days. If the spontaneous sensitization of man to horse serum was the result of prior contact with serum then one should have expected, at least in this case, a definitely shortened incubation period to three or even five days just as it is shortened after reinjection of serum as von Pirquet showed.

Summary. This comparative study of the clinical and serologic features of the three types of serum sensitiveness—the anaphylactic guinea pig, man after serum disease and spontaneously allergic (asthmatic) man—has indicated the significant similarities and differences in these allergic states. It appears that animal anaphylaxis and serum disease are identical from an immunologic point of view, whereas the naturally serum-sensitive man shows by the complete absence of precipitating and muscle-sensitizing antibodies a distinction that may well be fundamental. The existence and average quantitative relationship of these three antibodies are tabulated as follows:

Type of Allergy	*Type of Antibody*		
	Skin-Sensitizing	Muscle-Sensitizing	Precipitin
Anaphylaxis	+	+++	+++
Serum Disease	++	+++	+++
Asthma	+++	0	0

Functions of Antibody. It is generally agreed that there is a reason for cellular activities that are normal and usual and this also obtains for those newly acquired under special stimulation, hence this may be assumed to be the case for the production of antibodies leading to the allergic state. For good or ill there is a reason for their being. The antibodies in the allergic state have been considered and specified. For what appear to be sound reasons it has been postulated that these three antibodies are separate and distinct; each has its own properties and functions. The smooth muscle and the skin-sensitizing antibodies have a somatic specificity indicated by their name, just as they also have antigenic specificity. Precipitin has antigenic specificity but no tissue affinity and is therefore a purely humoral antibody. This is not in agreement with the generally accepted unitarian theory of antibody, but further supporting evidence is given in Chapter 3.

This hypothesis has definite appeal when one considers these antibodies in relation to their function and to the clinical and serologic evidences of their activity. It is agreed that allergic (anaphylactic) reactions are the results of antigen-antibody union upon or within the cell. A necessary corollary to this would seem to be that a reaction involving sensitized cells must express itself clinically by such responses as the sensitized cell is capable of; hence sensitized skin evidences its reaction in edema and hyperemia (wheal formation), whereas the sensitized muscle is stimulated to contract. The result is that there is urticaria (edema) in serum disease and in the naturally serum-sensitive man, and bronchial contraction with asphyxia in the anaphylactic guinea pig and probably also in man (post-serum disease) if conditions are right.

Precipitin acts to bind precipitinogen. Its presence in quantity is followed by the prompt disappearance of antigen from the blood as Longcope and Rackemann[16] showed. Its function then is to rid the body of the foreign substance for which it is specific, or at least this is a step in its elimination. It has no somatic affinities hence no tissue effects.

According to this conception production of histamine would therefore take place primarily in sensitized tissue and exert its pharmacologic effect locally. Excess histamine, if produced, might then be liberated and exercise a systemic effect. This seems unlikely in man for as Rose[25] has said, "although it is possible that histamine may be released in the types of allergic disease (asthma, urticaria, vasomotor rhinitis, etc.) studied in the present communication, the results of the above observations do not warrant such a conclusion." A clinical observation to support this is the absence of dyspnea (asthma) as a general characteristic of the syndrome of acute and extensive serum disease.

Diagnosis

In arriving at a diagnosis the first question is whether or not one is dealing with an allergic condition, and, if so, what is the specific cause of the signs and symptoms of which the patient complains. The answer to these queries is obtained only as a result of a study which comprises a detailed and intimate history, physical examination, laboratory tests, special skin tests and certain clinical observations to test the accuracy and completeness of the diagnosis.

History. This is probably the most important single procedure and must be complete, that is, it must be a careful and detailed medical survey of the family lineage, ascending and descending alike, with particular reference to allergic diseases. The habits, environment and contacts of the patient and his past and present illnesses should be noted. This is best done by using some such form as shown in the subsequent outline (p. 37). I do not believe in a history sheet to be checked or answered yes or no, but a questionnaire used merely as a constant reminder is essential for a well-written history to avoid overlooking some of the vital data. It cannot be emphasized too strongly that an adequate history is more than half the diagnostic battle and no history can be properly detailed at a single interview. It must be gone over again and again. The antecedent history is significant on account of the hereditary factors in many allergies. The contacts at home, at work or play are important because the allergen so often is derived from some external source, something eaten, inhaled or touched. The story of past illnesses and other allergies may give clues toward the cause of existing symptoms and disclose evidences of systemic disease other than allergy. In allergic disease the present allergy is too frequently one of long standing and consists of isolated clear-cut attacks of the sort for which the patient is seeking relief, or a gradually developing syndrome of exacerbations and remissions of symptoms of unexplained origin. Both training and experience are required to secure a good history.

Physical Examination. This must be complete for all new cases and should be repeated at least once a year. It means that height, weight, pulse rate and blood pressure are taken, the heart, lungs, abdomen, extremities and skin are examined, and finally, a careful examination is made of the oral and upper respiratory tract. Every physician should acquaint himself with the use of the nasal speculum and pharyngoscope as well as the otoscope and ophthalmoscope. He should inspect the teeth and gums in order to recommend expert dental opinion if indicated. Foci of infection are of utmost importance in the bacterial allergies and are found primarily in the upper respiratory tract in at least nine out of ten cases.

Laboratory Examination. With the information from the history and physical examination, the physician should then decide what additional information is required. It is my practice at this stage to list the various clinical and laboratory tests and other consultations required for the individual case. These are intended to disclose the patient's general physical condition, the presence or absence of an allergy and ultimately its cause.

Skin Tests. These are dealt with in Chapter 31. In general it may be said that skin tests are a valuable adjunct in the etiologic diagnosis of certain allergies provided active standardized extracts are used and the tests are carefully done, adequately checked, and properly interpreted. A complete reliance on skin tests without relating the reacting allergen to the clinical allergy has been one of the principal causes of error in diagnosis. Skin testing, aimless, excessive and misunderstood, has done more than its share in bringing allergy into disrepute.

As stated elsewhere,[26] it must be remembered that with these tests one must duplicate the essential histologic characteristics of the existing lesion. The type of test, ophthalmic or dermal, intracutaneous, scratch or patch, direct or indirect, must therefore be selected for the type of case and for the individual patient.

Evidence Indicating Allergy. If several of the following points appear after a study such as that indicated there is presumptive evidence of allergy.

(1) A history of antecedent allergy, either direct or collateral, with allergy in brothers, sisters or children, in other words a familial incidence.

(2) A history of other definite allergies in the patient, either past or present.

(3) A long-standing history of recurrent attacks at longer or shorter intervals or a continuous symptom complex not adequately explained on any other medical basis.

(4) The presence of blood eosinophilia, not attributable to intestinal parasites.

(5) Well marked positive skin tests properly confirmed. These definitely indicate an allergic constitution, even though they cannot be interpreted as being of causal significance, but they must be genuinely positive tests, not merely slight irritative reactions so often seen in many skins.

(6) The existence of definite symptoms frequently present in many of the accepted diseases of allergy.

Clinical Tests. Except in the simple straightforward cases such as hay fever, where the skin test fits the patient's history accurately, the physician should, after what appears to be a logical diagnosis of the cause, try to prove the truth or falsity of his opinion by relieving and reproducing the patient's symptoms by means of the clinical test of avoidance of and contact with the suspected allergen. The attempt to verify the accuracy of one's diagnostic acumen is a procedure not used often enough. An etiologic diagnosis of allergy must be supported by appeal to the common sense of both patient and physician.

With patients in whom no causative factor is definitely determined after the most careful investigation but in whom the presumption of allergy remains, one is entitled to and should use the clinical method of trial and error. This is done by resorting to *environmental change* or dietetic restrictions. However, an improvement or disappearance of the allergic syndrome after such procedures should not be taken as complete proof of the cause unless the symptoms can be made to appear and disappear on *three* successive trials under identical conditions. This has been my established practice for many years and by its use false hopes and diagnostic pitfalls have been avoided.

In the use of *dietetic* restrictions one may use the elimination diets of Rowe,[27] although individually improvised restrictions are entirely satisfactory. Patients must be warned that these diets are not meant for long continued use but only for limited diagnostic trials, for they are not based as a rule on the caloric, protein, mineral or vitamin requirements of the patient and may, if persisted in, lead to malnutrition and deficiency disease.

Outline of Diagnostic Allergy Study. It is not possible in an outline, nor for that matter even in a book, to specify the details necessary to elicit all the information needed for diagnosis or to develop the intuitive sense that comes only with experience and careful training.

This outline for a diagnostic study covers allergic diseases in general and is not meant to be used in its entirety in every and all definite or presumed allergic conditions. The history of a simple seasonal coryza may be brief but it is important to know if "winter colds" are frequent or if a mild perennial rhinitis also exists, whether "shrinkage" sprays and nose drops are being used and if so how often. The history for a diagnosis of asthma or eczema or angioedema may be very complicated, demanding more exhaustive inquiry into the various contacts, the relation to environment and the associated infections.

In asthma it is often difficult to evaluate the extent of disability. This may be determined by questions as to the amount of time lost from school or work, or one may question regarding the amount of symptomatic medication required by day and night, for adults will often say they lose no time at work or no sleep but inquiry discloses this is because of frequent ephedrine medication or epinephrine inhalation. This is a useful practical point.

I do not believe it necessary or possible to insert all the various questions that naturally develop on some positive fact. For example, when the patient says he cannot eat a certain food one should ask why, for it may turn out that his abstinence is due not to his own sense of its harmful effect, as I have found too often, but to a physician's mandate on the basis of some skin test or on no discoverable basis at all. One should ask what symptoms followed and how soon after ingestion. If one hour one time and twelve hours another, it is clear that this food has no causal relationship.

In the matter of laboratory examinations, skin tests and consultation services, certainly not all of those shown in this outline are necessary for each patient. In a case of uncomplicated hay fever it is not necessary to make a complete physical examination, though this is wise, but certainly a complete survey of the upper respiratory tract is essential. If such examinations were made in seasonal and perennial rhinitis cases there would be more early diagnoses of sinusitis predisposing to a later asthma.

The character and number of the tests, laboratory and otherwise, and the type of consultation service is determined by the history and physical examination. Those frequently used in a complete diagnostic study are outlined here. It is a good practice to make a list of those indicated by the history and physical examination and then see that they are carried out. Such procedures lead to more accurate and complete diagnoses.

HISTORY QUESTIONNAIRE. A Memorandum of Points that may be used in the Diagnostic Study.

Name .... **Address** ....

Age .... **Sex** .... **Race** .... **M.S.W.** .... **Occupation** ....

Chief Complaints: Summary.

Chief Allergy. Symptoms and age at onset.
Perennial or seasonal.
(Date of onset and offset).
Environmental or not.

Associated Allergies: Known reactions to animals, foods and drugs.

Infections: Recurring respiratory or other acute infections.

Family History:
- For Allergies Past and Present:
  - In father and father's family.
  - In mother and mother's family.
  - In brothers and sisters.
  - In offspring.
- For other Diseases of Significance: e.g., Tuberculosis, vascular disease, carcinoma and diabetes.

Personal History:
- Foods: Those regularly eaten, those not eaten and why.
  - Any unusual dietetic habits. Any known allergic reactions to foods. (Details.)
- Drugs: Habitually used and any known allergic reactions. (Details.)
- Contacts:
  - At home: animals, dusts, beddings, cosmetics, insecticides and plants.
  - At work.
  - Occasional and special contacts.
- Digestion.
- Bowel Activity.

Headache: Character—Location—Frequency—Duration.
Fatigue: Physical and nervous.
Weight: Recent gain or loss.
Dental care.
Exercise.
Tuberculin and Schick Tests: Results with details and dates.
Immunizations: Diphtheria, smallpox, tetanus, typhoid and pertussis or any others, with details and dates.
Therapeutic Serum Injections: Details and dates (serum disease?).
Past Illnesses:
- Other Allergies: Description and dates.
- Other Diseases.
  - Infectious: bacterial, viral, spirochetal, rickettsial, fungous, as well as protozoan and animal parasite infections.
    - *Note:* Special attention should be paid to the contagious diseases of childhood, infections of the respiratory tract as "colds," tonsillitis, bronchitis, and sinusitis, as well as to dental infections.
  - Systemic: gastro-intestinal, respiratory (sinusitis), renal, cardiac, pelvic, dental and glandular.
- Operations: especially nose and throat, with details and dates.

Present Illness:
- Its symptoms and any known cause.
- Age at onset.
- Season: Date of onset and offset.
- Relation to: Environment, exertion, exposure to heat or cold, acute infection, occupation, menses and pregnancy.
- Description of early attacks: Symptoms, frequency, duration and development of the present attack.
- Description of recent attack: Symptoms, frequency and duration.
  - Amount of disability due to attacks.
  - Relation to diet, environment and acute infection.
  - Known contacts inducing attacks.
- Past investigations, treatments and results.
- Present symptomatic treatment, if any, with details as to character of drugs, frequency and amount used.
- Present specific treatment, if any, with details.
- Other existing allergies not related to the chief allergy, give details.
- Associated Diseases: Cardiac, renal, arthritic and glandular (diabetes and thyroid).

Physical Examination should include:

- General appearance, weight and height.
- Eyes, ears, teeth.
- Nose and throat.
- Heart, blood pressure, pulse rate.
- Lungs, vital capacity.
- Abdomen, extremities, skin.
- Rectal and pelvic examination in special cases.

Laboratory Tests Frequently Required:

Note: Those indicated in the individual case should be listed after the physical examination and checked when done.

- Blood: Leukocyte and differential counts and hemoglobin determination.
  - Chemistry (if indicated).
  - Sedimentation rate of erythrocytes.
  - Wassermann or Kline tests.
- Smears: Sputum for eosinophils, fungi, spirochetes and tubercle bacilli.
  - Nasal and antral discharges for pus and eosinophilia.
  - Skin for bacteria and fungi.
- Roentgenograms:
  - Chest—6 foot plate or stereoscopic.
  - Lipiodol bronchogram.
  - Pharynx—soft tissue
  - Sinuses—plain and with umbrathor or lipiodol.
- Cultures: Sinus irrigations, tonsils, sputum or laryngeal swab, teeth, tissues from tonsil, adenoid and sinuses, and skin.

Allergen Tests: Method and extent to be decided by the age of the patient and the character of the allergy.

- Skin Tests: Intradermal (direct or passive transfer).
  - Scratch.
  - Prick.
  - Patch.
- Ophthalmic.

Clinical Tests:

- Environmental.
- Diet—restrictive.
- Drugs.

Tuberculin and Schick Tests.

Immunizations required: Diphtheria, tetanus, typhoid, pertussis and influenza.

Note: The child with active intrinsic allergic dermatitis (eczema) should never be given smallpox vaccine. There is considerable risk in using smallpox vaccine on anyone when another member of the same family or household has active dermatitis (eczema).

Additional Tests:

- Electrocardiogram.
- Circulation time.
- Venous pressure.
- Basal metabolism.
- Bleeding and coagulation time.
- Blood platelet count
- Capillary fragility (Tourniquet test).
- Vitamin assay

Additional Consultation Service:

- Rhinology—nose and throat.
- Bronchoscopy.
- Dentistry.
- Dermatology.
- Cardiology.
- Ophthalmology.

Prognosis in Allergy

In order to give a reasonably accurate prognosis for any existing allergic manifestation, whether artificially induced or spontaneously acquired, one must be cognizant of what it means to be or become sensitized and what is the usual or frequent course of events in the person who has once evidenced an allergic manifestation.

Those in whom an allergic state has been artificially produced by the therapeutic use of antitoxic serum usually lose this sensitization in the course of a relatively few months. Those who have developed a sensitization after the prolonged use of an antigenic substance such as liver extract or insulin or have developed dermatitis to dye or plastics are apt to remain allergic for years.

Most of the spontaneous diseases of allergy occur in the group in whom hereditary or familial influences are significant. It seems a proper deduction that in all such cases the allergy represents a constitutional defect. This is borne out by what may be spoken of as the life history of allergy in these predisposed individuals.[9] The infant who has an acute gastrointestinal and systemic allergy due to egg or milk or the one who has developed dermatitis will, as a rule, lose this particular sensitization before the age of five years. A study of case histories shows that a majority of such infants will develop an allergy of some type (usually asthma or hay fever) and to a different allergen in childhood or early adult life, and these sensitizations are then carried as a rule through life to an advanced age.

What this means is that the hereditarily acquired sensitized state is a problem that has to be considered through life and gives point to the statement—once an allergic always an allergic.

It is obvious therefore that the prognosis, as far as a loss of the spontaneously developed state of sensitization is concerned, is not favorable and must be so recognized by the physician. However, there is a great difference between the allergic state and allergic disease. The patient is not concerned with the existence of the former but only with its resultant symptoms, and here the prognosis will depend upon diagnosis and management.

In general, it may be said that the earlier an allergy is recognized as such, completely diagnosed and adequately treated as to the cause, the more favorable is the outcome in so far as the manifestations and the sequelae of uncontrolled allergy are concerned. A prognosis then, although it may be optimistic as to symptomatic prevention under accurate diagnosis and proper care, must always be guarded as to cure because sensitization once established is liable to persist.

The prognosis of the various diseases of allergy will be taken up in the appropriate chapters.

Preventive Treatment

Obviously symptomatic treatment is indicated whenever possible for all allergic diseases and specific therapy, based upon an etiologic diagnosis, is carried out by avoidance or removal of the cause and by specific injections. The following discussion is concerned with the possibilities for the prevention of the development of allergic states in so-called normal persons devoid of allergic background, and in the group that have family or personal evidence of sensitization.[28] The prevention of the allergic manifestation once sensitization is established is a part of treatment and is considered under the various allergic diseases.

(1) **The Non-Allergic Group.** The fact that a few non-allergically disposed individuals, so-called normals, develop a sensitization after long or shorter exposure to sensitizing chemicals and dusts, expressed usually as a dermatitis and occasionally as asthma, does not warrant unusual precautions other than that of lessening contact through personal and environmental cleanliness (as recommended by Schwartz and Tulipan)[29] especially when engaged in the so-called likely industries.

Certain synthetics such as plastics and dyes that are active sensitizers and have appeared on the market for public use should be and are quickly withdrawn, as was done with the "glaselastic" a few years ago. Certain drugs such as sulfonamides are important largely because of their extensive use and the serious effects of the resultant allergies. Although sensitization to them does not occur in a large percentage of patients, the sulfas should be used with caution and only on definite indication.

Chronic foci of infection that are a source of continuous absorption of bacteria or their products are as great, if not greater, in importance than the chemicals mentioned, for they act not only as sensitizers but as the underlying cause of many of the inflammatory and degenerative diseases of man. Preventive medicine demands their discovery as well as their proper management as one means of avoiding illness including allergic disease. These foci of infection are present and discoverable years before symptoms appear in a large percentage of those supposedly non-allergic persons who develop asthma after forty years of age.

(2) **The Allergic Group.** There are some measures that should be discussed that bear on the prevention of the development of sensitization in those who may be spoken of as the allergically predisposed by reason of lineage or because of the evidence of a personal allergy, even though a minor one. The possibility of an approach through the application of the principles of eugenics is impractical and impossible both on account of the ignorance of the physician and public opposition, although it is known that the marriage and especially the intermarriage of allergic persons does increase the number of allergic offspring. It is possible, however, to limit and control certain contacts for this predisposed group

of individuals, especially infants and children, without disturbing too much the usual course of life.

Foods. For the allergically predisposed infant Pounders[30] suggests that, on general principles, cow's milk should at first be boiled, dried or condensed, to lessen the antigenic activity of the proteins. Raw vegetables and fruits, as tomato and orange, should be given sparingly. Overfeeding is to be avoided.

Some months after birth an idea of the future course of events may be obtained by serologic study, for in our work on infant sensitization by the method of passive transfer it was amazing to find in infants with allergic dermatitis how frequent were the number of definite skin reactions to allergens not yet active in the production of symptoms. Contact with these discoverable reacting substances should be avoided and such a study gives point and purpose to the restrictions that should be imposed. If in spite of the best efforts clinical sensitization actually develops, as well it may, an early diagnosis and treatment are indicated and to this point of view both physicians and the laity must be educated, for long continued allergic disease may lead to secondary effects that affect health and limit activity. It is to the prevention of such results that prophylactic therapy and early diagnosis and treatment are directed.

Drugs. As far as drugs are concerned, at all ages one must be careful about those now regarded as having a high sensitizing capacity, as the sulfonamides, those giving dangerous clinical reactions, as aspirin, and one must be particularly cautious of all intravenous medication, especially the iodides, quinine, and certain complex amines such as diodrast.

Inhalants. There is little reason to question the advisability of minimizing the air-borne allergens for the predisposed infant and child. The home, the child's room, and especially the bedding, should be clean and kept clean. Toilet powders containing orris or rice and insecticides should not be used. Dogs, cats, birds are taboo. They must not be allowed in the house. Fathers who work at dusty jobs as millers, bakers and hostlers must avoid carrying occupational dusts to the home.

If asked for definite proof that all these precautions against foods, drugs or inhaled dusts are really worth while preventive measures against the development of sensitization, the answer would have to be that there is no such evidence. However, this much can be said, that if such contacts are not at hand at least attacks cannot be precipitated by them even though they have not prevented the sensitization.

Reasonable measures of dieting as suggested, diets that protect against undernourishment and deficiency disease, together with common sense measures for the abatement of dusts of all sorts, can be readily used in the homes of allergic families. With regard to outdoor dusts, such as pollen and molds, nothing practical can be done as a preventive step. Once the trouble has started measures may be taken to control the duration and degree of exposure by any one of the several types of air conditioners that were and will again be commercially available.

Infection. With regard to control of infection as a preventive measure one may speak more definitely. In the allergically predisposed, the more infection the more allergy there is likely to be. Such infants and children should receive every protective measure the pediatrician has to give, protection against pertussis, diphtheria, tetanus, measles and the ordinary acute respiratory infections. Although infected parents constitute an insoluble problem, children should be protected against nurses with chronic sinusitis and bronchitis just as much as against those with tuberculosis.

Children with recurring colds and infected tonsils and adenoids should have them removed at the earliest favorable time, generally at two to three years of age. When possible it should be done before the first attack of asthma. In older children and adults foci of infection should be discovered early and treated or removed if possible before an allergy becomes established. This is discussed more fully under infective asthma (Chapter 7). As contributory to upper respiratory infection, the nasal allergies, both perennial and seasonal, are very important and while they deserve therapy for their own sake, specific treatment is an important step in the prevention of acute and chronic nasal infection, as Sternberg[31] has pointed out.

Besides such measures all allergically disposed patients, especially infants and children, should be protected and protection maintained against the possible future need for various antiserums through immunization with diphtheria and tetanus toxoids regardless of whether they are or are not skin-sensitive to animal serums.

To sum up what has been said: (1) In non-allergic families no unusual preventive measures are indicated. (2) In the offspring of allergic parents certain reasonable steps should be taken. It is the duty of the specialist in allergy to instruct parents, patients, the family doctor and the pediatrician on all practical preventive measures that are indicated in these allergic families. (3) Foods that are usually eaten raw should be used infrequently. (4) In regard to inhalant contacts nothing that is vital is restricted in the few suggestions made. (5) Infections of all types should be guarded against.

Proper attention to nutrition, environment and infection, preventive as well as therapeutic, is what constitutes the difference between the physician in allergy and the skin-testing specialist. Actually and practically the preventive steps taken are directed to the prevention of the symptoms once the allergic state has been set up. This means early and accurate diagnosis of the cause whatever it may be, followed by carefully directed avoidance or specific treatment of the cause, or both as called for, together with proper attention to the patient's general welfare. These will be discussed in the several chapters on allergic disease.

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3. *Special Serologic Features of the Immediate Wheal-Reacting Allergies*

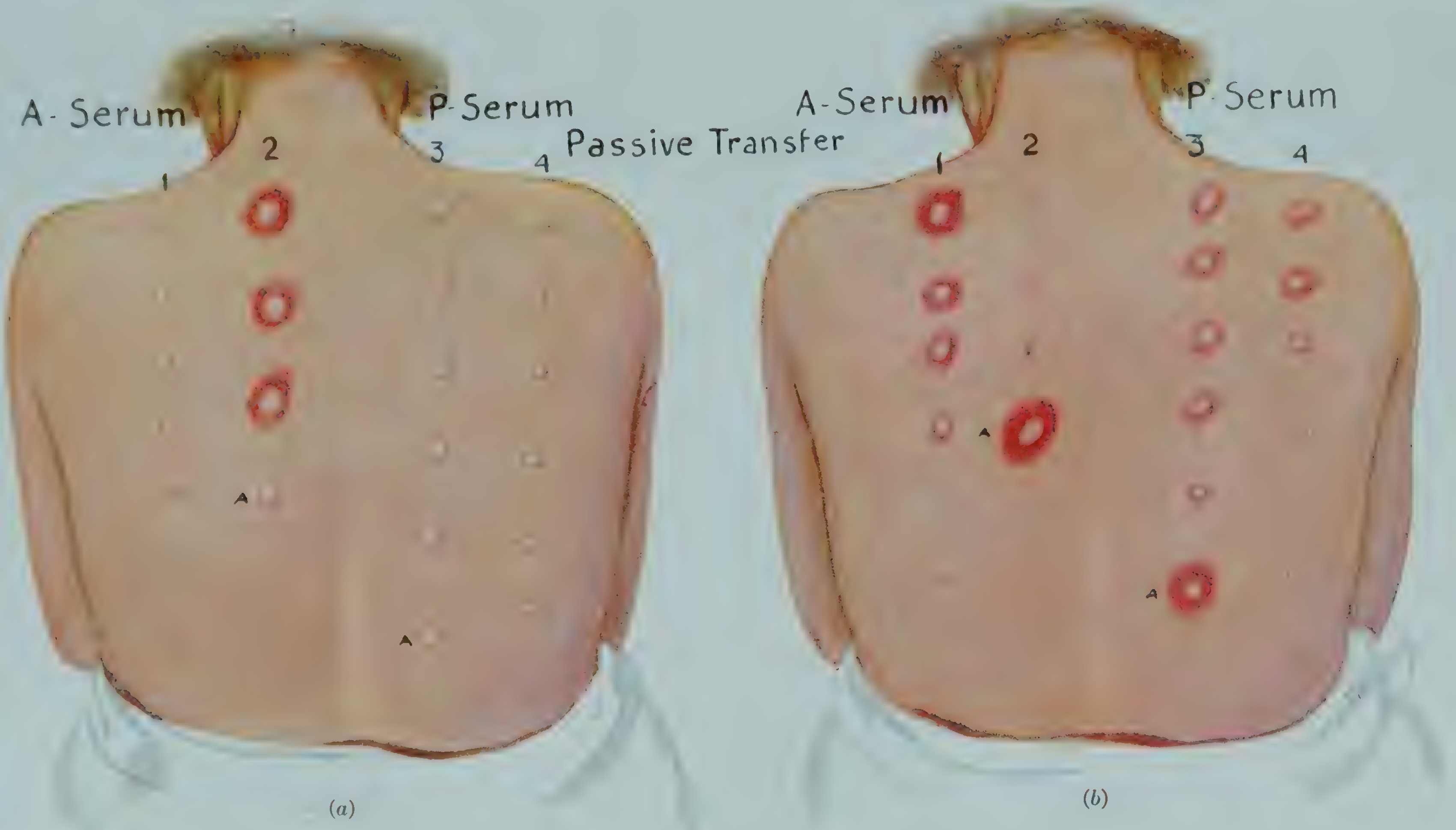
ROBERT A. COOKE

POLLEN hay fever is typical of the immediate wheal-reacting allergies. On account of its frequency and the resulting availability of patients, it is the allergy on which the following serologic studies have been made. From observations on similar immediate wheal type allergies such as asthma, due to other antigens, as animal danders, there is little reason to doubt that the findings in the one are applicable to the others of this class.

The object of the serologic studies has been to obtain additional information on the many questions to which there still are no adequate answers. For example, it is known that a positive skin test is not a criterion of clinical sensitiveness but it is not always known why this is so. Again there is no complete explanation for the mechanism of protection or immunity that results from the injection of antigen in the skin-reacting allergies, although from clinical study it is known that protection is afforded. Further, the results of treatment in hay fever still leave much to be desired, for there are many problem patients such as those that do not respond to injections and those in whom systemic reactions frequently occur.

These studies were made using the procedure of passive transfer of sensitiveness. Two different modifications of the passive transfer test were employed. The *dilution test* is carried out through the use of serial dilutions of a sensitizing serum. Sites are made by the injection of 0.1 ml. of the various dilutions of serums into the skin on the back of a normal test subject (Fig. 2 (*a*) 1 and 4). Two days later these sites are tested with the antigen (Fig. 2 (*b*) 1 and 4). By the highest dilution titre which produces a prompt response to this test, the amount of antibody and probably its activity in the serum may be determined. Serum from some patients when diluted several thousand times gives a reaction to an antigen.

In the *neutralization test* a fixed amount of sensitizing serum is mixed in vitro with known graduated amounts of the antigen and allowed to stand overnight at icebox temperature. These "mixtures" in definite volume are injected into the skin of normal test subjects and the immediate reaction, if any, is noted (Fig. 2 (*a*) 2 and 3). After forty-eight hours, these sites are tested with a definite volume and strength of antigen (Fig. 2 (*b*) 2 and 3). The object of this test is to determine



(*a*)

(*b*)

Fig. 2. –The results of dilution and neutralization tests by passive transfer as recorded in Table 1
(*a*) Immediate reactions read at the time sites were made.
(*b*) Immediate reactions read at the time sites were tested forty-eight hours later.

TABLE 1

Comparison of Ante- and Post-Treatment Serum (Busch)

Test Subject DL

Dilution Tests		*Neutralization Tests*			
		Mixtures made with Equal Amounts of‡		Reaction of Sites	
Serum Dilutions*	Reaction to Test†	Busch Serum	Ragweed Units per ml.	1 hr. after Sites Were Made	On Retest§
Ante-treatment	Fig. 2 (*b*) col. 1				
1:10	+++	Ante-treatment	50	+++	0
1:100	++	" "	100	+++	0
1:200	++	" "	150	+++	0
1:300	+	" "	Saline	0	++++
1:500	±				
Post-treatment	Fig. 2 (*b*) col. 4	Post-treatment	150	0	++
1:10	++	" "	300	0	++
1:100	++	" "	500	0	++
1:200	+	" "	700	0	++
1:300	0	" "	1000	±	+
1:500	0	" "	Saline	0	+++

* 0.1 ml. of the serial dilutions of serum in physiologic saline was injected into each site. (Fig. 2 (*a*) cols. 1 and 4.)

† The serum dilution sites were tested 48 hours later with 0.025 ml. of ragweed extract. (100 P.N. units per ml.) (Fig. 2 (*b*) cols. 1 and 4.)

‡ 0.1 ml. of these serum-ragweed or serum-saline mixtures was injected into each site. (Fig. 2 (*a*) cols. 2 and 3.)

§ The serum-ragweed or serum-saline mixtures were tested 48 hours later with 0.025 ml. of ragweed extract (100 P.N. units per ml.). (Fig. 2 (*b*) cols. 2 and 3.)

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whether or not the amount of antigen in the mixture used up, that is neutralized, any or all of the skin-sensitizing antibody in the "mixtures."

Using these simple tests to compare the serum of a patient before any treatment (ante-treatment or A-serum) with the serum of the same patient after treatment (post-treatment or P-serum), it was possible to observe any alteration that had occurred as a result of the injection of the antigen used in the treatment. From such comparative studies illustrated by Table 1, it was apparent that the amount of ragweed pollen antigen needed to neutralize the antibody of the post-treatment serum was out of proportion to the amount of *skin sensitizing-antibody* shown by the dilution test, suggesting the presence of a second immune body in the serum, the *blocking antibody*, as I originally called it.[1]

The Skin-Sensitizing Antibody

Dominant Antigens. In patients with allergies giving the immediate test wheal it is common to find reactions to many related and unrelated allergens. It has always been a question whether or not there was a separate antibody for each of the allergens.[2] Patient WOL is an example of a patient who gave twenty-two reactions on direct test with various antigens. On passive transfer his serum gave an identical response to all these biologically related and unrelated test solutions, as shown in Column II (Table 2, page 50). His serum, previously mixed with ragweed extract, was injected into twenty-two other sites on the back of the normal test subject. These areas or sites were tested with the twenty-two antigens after a lapse of forty-eight hours. Column I (Table 2) shows that the ragweed extract neutralized the antibody in the serum for all of the allergens but two, plantain and sorrel. This result shows that ragweed was a "dominant" antigen. Plantain and sorrel were also dominant in this patient (WOL) who was clinically sensitive to and had hay fever from plantain, sorrel and ragweed.

It has long been known that the skin-sensitizing antibody titre is often increased after antigen injections. Sherman[3] demonstrated this was particularly evident early in the course of the specific treatment. That this was true for the WOL serum after injections of ragweed extract is shown in Table 3. As determined by the dilution test, the amount of antibody for ragweed was increased four-fold, that is, the test was positive at a dilution of 1:1000 before treatment and at a dilution of 1:4000 after treatment. The interesting and significant point was that the antibody for plantain was also increased fourfold from 1:500 to 1:2000. This was the result after the patient (WOL) had injections of ragweed extract alone, not plantain, and in spite of the fact that plantain was a dominant antigen since the antibody-combining group for plantain was not neutralized by ragweed extract.

That this is not an unusual finding is indicated by the corresponding increase of antibody for the separated Fraction 1 and Fraction 2 derived from whole ragweed pollen (see Chapter 11). It is not indicated here to give the chemical and biological evidence for the existence of such independent proteins. Suffice it to state that Stull et al.[4, 5] have separated them. Our present studies concern only Fractions 1 and 2. Fraction 1 has the characteristics of a plant albumin precipitable at 50 per cent saturation with ammonium sulfate, with trichloracetic acid and with phosphotungstic acid. It is heat labile. Fraction 2 precipitates between 50 and 100 per cent saturation with ammonium sulfate and with phosphotungstic acid but not with trichloracetic acid. It is heat stabile and behaves like plant proteoses. One patient (KAN) reactive to both Fractions 1 and 2 of ragweed pollen was treated with injections of Fraction 1. When his ante- and post-treatment serums were compared on passive transfer dilution test a threefold increase of antibody was

TABLE 2

Neutralization by Ragweed Extract of Various Allergens that React with an Ante-treatment Serum (WOL) in Passive Transfer Sites

		Column I	Column II
Sites	*Tested With*	*Reaction in Serum-Ragweed Sites**	*Reaction in Serum-Saline Sites†*
1	Low Ragweed Pollen	0	++++
2	Marsh Elder “	0	+++
3	Mugwort “	±	++
4	Cocklebur “	0	+++
5	Plantain “	++	++++
6	Sorrel “	++	+++
7	Timothy “	0	+++
8	Orchard Grass “	0	+
9	Ash “	0	+++
10	Birch “	±	++
11	Alder “	0	+++
12	Elm “	0	++
13	Hickory “	0	++
14	Poplar “	0	+
15	Sweet Gum “	0	++
16	Pyrethrum	0	++
17	Orris	0	++
18	Alternaria	0	+
19	Lycopodium	0	+
20	Cottonseed	0	+
21	Flaxseed	0	++
22	Kapok seed	0	++

* 0.1 ml. of a mixture of equal parts of WOL ante-treatment serum and low ragweed extract (100 protein nitrogen units per ml.) was injected into the skin of a normal test subject in each of 22 sites and tested 48 hours later with 0.025 ml. of each of the 22 allergens. (1000 protein nitrogen units per ml.). Reactions were recorded after 15 minutes.

† As controls, 0.1 ml. of a mixture of equal parts of WOL ante-serum and saline was similarly injected into the skin in each of 22 other sites and tested 48 hours later with the same 22 allergens. Reactions were recorded after 15 minutes.

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found in the post-treatment serum for Fraction 1 and exactly the same increase for Fraction 2 which had not been used in treatment (Table 4). The reverse is seen in patient NEZ, reactive to both fractions but treated with Fraction 2. Here there was a tenfold increase of antibody for Fraction 2 in the post-treatment serum and a similar increase for Fraction 1 which was not used for treatment injections. (Table 5.)

TABLE 3

DILUTION TESTS WITH WOL SERUM TAKEN BEFORE (A) AND AFTER (P) RAGWEED INJECTIONS*

Dilution in Saline	*Reaction on Test With:*	
	Low Ragweed	Plantain
WOL Serum A		
1:500	++	+
1:1000	±	0
1:2000	0	0
1:4000	0	0
WOL Serum P		
1:500	+++	++
1:1000	++	+
1:2000	+	±
1:4000	±	0

* The duplicate sites with serum A and serum P were made by the injection of 0.1 ml. of serum and saline in the dilutions stated into the skin of a normal test subject and tested 48 hours later with 0.025 ml. of ragweed in one series of sites and plantain pollen extract in the duplicate sites, each 1000 protein nitrogen units per milliliter. Sherman, W. B.: J. Immunol., *40:*289, 1941.

TABLE 4

DILUTION TESTS WITH KAN SERUM TAKEN BEFORE (A) AND AFTER (P) TREATMENT WITH LOW RAGWEED FRACTION 1*

Dilution in Saline	*Reaction to Test with 1000 Protein Units of:*	
	Fraction 1	Fraction 2
KAN Serum A		
1:30	+++	++
1:100	+++	++
1:300	++	+
1:1000	±	+
1:3000	0	0
KAN Serum P		
1:30	++++	+++
1:100	+++	+++
1:300	+++	++
1:1000	++	+
1:3000	±	±
1:10,000	0	0

* The general procedures are exactly comparable with those previously stipulated at the foot of Table 3.

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TABLE 5

Dilution Tests with NEZ Serum Taken Before (A) and After (P) Treatment with Low Ragweed Fraction 2*

Dilution	*Reaction to Test with 1000 Protein Units of:*	
	Fraction 1	Fraction 2
NEZ Serum A		
1:10	++	++
1:30	±	±
1:100	0	0
1:300	0	0
1:1000	0	0
NEZ Serum P		
1:10	+++	+++
1:30	++	++
1:100	+	+
1:300	±	±
1:1000	0	0

* The general procedures are exactly comparable with those previously stipulated at the foot of Table 3.

These observations make it seem probable that for the skin-sensitizing antibody there is but one basic unit so to speak, but with different combining groups on the same molecule, at least two on the antibodies in the serum of WOL, one for ragweed and those other antigens neutralized by ragweed, and another for plantain and sorrel. (Table 2.)

This concept is contrary to accepted ideas for the precipitating antibodies on which the immunologists have centered their attention. A comparable situation with multiple precipitins following artificial immunization of the experimental animal is found in the work of Hektoen and Boor[6] and is presented in Table 6 rearranged from their published data. It is obvious there is no such thing as a dominant antigen here for there is no loss of specificity though there are occasional divergent or extra-specific reactions. Each one of the many antigens called forth or was responsible for its own precipitin which carried but one specific combining group on each antibody molecule.

Specificity of Antibodies. By comparing Table 6 with Table 7, which is similarly arranged and shows the neutralization tests on the serum of a patient (WOL) with multiple skin-sensitizing antibodies, a striking contrast is seen between the specificity of artificial multiple sensitization as determined by the precipitin test and the lack of specificity in the skin-sensitizing antibodies derived spontaneously or naturally in man.

I have already mentioned that this lack of specificity has been noted after serum disease by Voss[7] and by Mackenzie.[8] It may be an inherent property of skin-sensitizing antibodies in man in contrast with precipi-

TABLE 6

Serum Adsorbed with	*Serum Tested for Precipitins with*												
	Hemoglobin of								Chicken		Proteins		
	Beef	Cat	Dog	Hog	Horse	Human	Sheep	Turkey	Blood Albumin	Ovalbumin	Bence-Jones	Hogan	Horse Pseudoglobulin
Hemoglobin:													
Beef	0	±	±	±	±	±	0	+	+	+	+	+	+
Cat	+	0	+	+	+	+	+	+	+	+	+	+	+
Dog	+	±	0	+	+	±	0	+	+	+	+	+	+
Hog	+	+	0	0	+	0	+	+	+	+	+	+	+
Horse	+	+	+	+	0	+	+	+	+	+	+	+	+
Human	+	+	+	+	+	0	+	+	+	+	+	+	+
Sheep	+	+	+	+	+	+	0	+	+	+	+	+	+
Turkey	+	+	+	+	+	+	+	0	+	+	+	+	+
Chicken:													
Blood Albumin	+	+	+	+	+	+	+	+	0	+	+	+	+
Ovalbumin	+	+	+	+	+	+	+	+	+	0	+	+	+
Proteins:													
Bence-Jones	+	+	+	+	+	+	+	+	+	+	0	+	+
Hogan	+	+	+	+	+	+	+	+	+	+	+	0	+
Horse Pseudo-Globulin	+	+	+	+	+	+	+	+	+	+	+	+	0
Control	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++

Rearranged from Hektoen and Boor.[4]

TABLE 7

Composite Table of Passive Transfer Studies Showing Cross-neutralization Reactions with Ante-treatment Serum (WOL)*

Serum Mixed With	Reactions of Sites Tested With									
	Low Rag.	Sorrel	Plant.	Cockle.	Oak	Hick.	Birch	Poplar	Ash	Tim.
Low Ragweed	0	+	+	0	0	0	0	0	0	0
Sorrel	+++	0	±	+	±	0	0	0	0	0
Plantain	+++	++	++	++	++	±	±	0	±	0
Cocklebur	++	++	++	0	++	+	+	±	0	0
Oak	+++	++	++	+	±	+	0	+	0	0
Hickory	+++	++	+++	+	++	±	0	±	±	0
Birch	+++	++	+++	++	+++	++	+	+	++	+
Poplar	+++	++	+++	++	++	++	++	+	++	+
Ash	+++	++	+++	++	++	+	+	+	+	+
Timothy	+++	++	+++	++	+++	++	+	±	++	±
Control	++++	++++	++++	+++	+++	++	++	+	++	+
Dilution titre	±3000	±3000	+1000	+1000	±1000	±1000	±1000	±300	+100	+100

In the various experiments which are used to make up this composite table, the WOL serum was mixed with ragweed extract and ten different skin sites were made. After 48 hours one site was tested with ragweed and it was found neutral, that is, there was no reaction. Other sites tested with hickory, oak, birch, timothy, etc., also gave negative reactions and obviously had been neutralized by the ragweed antigen. On the contrary the sites tested with plantain still reacted, thus were not neutralized by the ragweed extract. In the same way WOL serum was mixed with sorrel or plantain or timothy, etc., and ten sites were made with these mixtures. Each site was then tested with the antigens enumerated and the results were as revealed in the above table.

* This table is arranged in the order of the dilution titre, that is, the reactivity as determined previously by passive transfer tests with the same allergens in serum sites of various dilutions.

This serum diluted 3000 times still gave slight reactions with extracts of low ragweed and sorrel, whereas with ash and timothy extracts no reaction was obtained after 100 fold dilutions.

Cooke, R. A.: J. Allergy, *15*:212, 1944.

tins. The case of WOL illustrates the multiplicity of skin test reactions that are devoid of clinical significance, but it does not explain the phenomenon. However, if further serologic studies of serum disease, for example, should confirm the essential differences in specificities between skin-sensitizing and precipitating antibody, then there would be further evidence against the unitarian theory of antibodies in addition to that which is presented in the discussion of the sensitizing and the blocking or neutralizing antibody (p. 57).

Clinical Significance of Dominant Antigen. In this connection another study is interesting and informative for it appears to indicate the significance of antigen dominance, which was suggested in the serum studies of patient WOL who was clinically sensitive to the dominant antigens but to no others. Sherman and Stull[9] showed that clinical reactivity in spontaneous allergy is related to this so-called dominance of antigen. In a patient asthmatically sensitive to dog and not to horse but reacting by skin test to both dog and horse danders, the skin-sensitizing antibodies in his serum were neutralized by dog but not by horse extract. In a contrasting case, asthmatically sensitive only to horse but reacting by skin test to both dog and horse danders, the horse extracts neutralized both antibodies while the dog extract neutralized only the antibody to dog. In a third patient in whom contact with dog and horse caused asthma, and whose skin tests were positive to both dander extracts, there was strictly specific neutralization between the antigen and the skin-sensitizing antibody in the serum. That is, the horse extract neutralized to horse, not to dog, and dog extract neutralized to dog and not to horse. There was no cross neutralization.

Dominance of antigen as determined by neutralization tests appears to be related to the clinical sensitivity or vice versa, and so seems to have some practical significance. However, an antigen is said to be dominant only in reference to a particular serum from a particular patient for no antigen is inherently dominant over another and there is no constant relation between antigens.

Individuality of Skin-Sensitizing Antibody. It is customary to think of ragweed hay fever and ragweed pollen sensitization as an entity. Clinically this is so, but serologically it is a different story. If one compares the serums of four typical ragweed hay fever patients as to their reactions and neutralizations to several related pollens the results disclose clear-cut variations in the antibody concerned. Table 8 shows that no two of the compared serums are completely alike in their reactions with other related pollens, or in the neutralization of these reactions by ragweed pollen antigen. From our studies, of which these are examples, the antibody in any particular serum when studied in detail with regard to reactions and neutralizations has what approaches a fingerprint individuality, a fact quite contrary to the general conception, which is based

TABLE 8

INDIVIDUALITY OF REACTIONS OF SERUMS FROM TYPICAL RAGWEED HAY FEVER PATIENTS

*Passive Transfer Sites**		*Reactions of Sites Tested with the Following Extracts†*							
Serum	Mixed with	Low Ragweed	Amaranth	Chenopod	Cocklebur	Iva	Mugwort	Sage	Russian Thistle
Hre.	Saline	++++	++	++	+++	++++	+++		++
Hre.	L. R. 1000 U.	0	0	0	0	0	0		0
Aar.	Saline	++	++	+++	+++	+++	++		++
Aar.	L. R. 1000 U.	0	+	+++	+	+	+		+
Wilk.	Saline	+++	++	++	++	++	+++	+++	
Wilk.	L. R. 1000 U.	++	0	0	±	+	++	++	
Elaz.	Saline	++++	+	±	+	+++	0	0	
Elaz.	L. R. 1000 U.	0	0	0	0	0	0	0	

---

* The four serums were each mixed with equal parts of saline or low ragweed (1000 protein nitrogen units per ml.) and 0.1 ml. of each such mixture was injected into the skin of normal test subjects to create sites for later testing.

† The sites were tested 48 hours later with 0.025 ml. of each of the diverse extracts.

NOTE: If one compares both the passive transfer test (serum and saline) and the neutralization test (serum and ragweed) of one serum with any of the other serums, it will be observed that no two of these sample serums behave exactly alike. For example, in Hre. serum, low ragweed neutralizes the antibody for all related reacting pollens and in Elaz. serum, the same result is obtained, but Elaz. serum has no sensitizing antibodies for mugwort which Hre. serum possesses.

Cooke, R. A.: J. Allergy, *15*:212, 1944.

on studies of artificially induced antibodies, for example, the specific results obtained by Hektoen and Boor in studies on artificially induced precipitating antibodies.

This evidence of the individuality of man based upon the properties and reactions of his skin-sensitizing antibody is especially interesting in view of the supporting indication of man's individuality as conceived by Landsteiner,[10] based upon the blood studies with the Rh factor and the sub-types.

The Blocking, Inhibiting or Neutralizing Antibody

The beneficial effect of pollen extract injections in hay fever patients as determined clinically has become an accepted fact. The reason for these results was not at all understood in 1931, when curiosity prompted Barnard and myself[1] to investigate the idea that it might be possible to secure evidence of a transferable immunity from treated to untreated hay fever patients by means of blood transfusion. A prompt and relatively lasting clinical improvement that was sometimes striking after the transfusion indicated the presence of some transferable protective body, the existence and nature of which it was hoped could be determined by serologic studies using the method of passive transfer. Only ragweed-sensitive hay fever patients were used.

A comparative study was made on the serum of patients taken before (A-Serum) and again after (P-Serum) intensive treatment with the ragweed pollen extract. Two types of tests were used, the dilution and the neutralization tests previously described.

The dilution test indicated the increase or decrease in the amount of the skin-sensitizing antibody. In the entire series of cases studied it was not strikingly altered, at times somewhat increased, especially in the early stage of treatment as stated, but generally decreased after long treatment.

The neutralization test with antigen-sensitizing serum mixtures, on the contrary, showed significant changes. The A-Serum ragweed mixtures when injected for sites in the test-subject gave immediate wheal reactions, whereas there was only slight or no reaction with P-Serum mixtures. At the end of forty-eight hours the same sites were retested with antigen alone and reactions were absent or slight in A-Serum mixture sites, but definitely positive in the P-Serum mixture sites. The results of a sample case are given in Table 1 (p. 48) and illustrated in Figure 2 (p. 47).

It was concluded from these observations that post-treatment serum contained an antibody which blocked or inhibited the reaction at the time the site was made with antigen-P-Serum mixtures thus leaving the skin-sensitizing antibody in the cell and available for reaction on test with the antigen forty-eight hours later. Confirmation of these results has been ample.[11, 12, 13]

Properties of Blocking Antibody. Further studies[14] on this blocking antibody showed that it may be produced in normal persons by the injection of an antigen without giving rise to any skin-sensitizing antibody (Table 9). Dr. Loveless[15] showed that it is thermostabile in contrast to the skin-sensitizing antibody which is destroyed by heat at 56° C. after four hours. Sherman, Hampton and Cooke[16] found that it readily permeates placental membrane and is present in cord blood, whereas it was shown earlier by Bell and Eriksson[17] and confirmed by us[16] that the skin-sensitizing antibody, with rare exception, is not transmitted from mother to fetus (Table 10).

TABLE 9

BLOCKING (INHIBITING) ANTIBODY IN A NORMAL PERSON (J)*

Skin Site on Test Subject	*Serum-Ragweed Mixtures for Sites†*		*Reaction at Site when Tested after 48 Hours with Ragweed Extract‡*
	Serum Combinations	Ragweed Units per ml.	
1	J serum A + H serum (ragweed sensitive)	50	++
2	“ “ “ + “ “ “ “	100	+
3	“ “ “ + “ “ “ “	200	0
4	“ “ “ + “ “ “ “	Saline	+++
5	J serum P + H serum (ragweed sensitive)	200	+++
6	“ “ “ + “ “ “ “	300	++
7	“ “ “ + “ “ “ “	400	++
8	“ “ “ + “ “ “ “	600	+
9	“ “ “ ± “ “ “ “	800	±
10	“ “ “ + “ “ “ “	1000	0
11	“ “ “ + “ “ “ “	Saline	+++
	Controls		
12	B serum + H serum (ragweed sensitive)	50	++
13	“ “ + “ “ “ “	100	+
14	“ “ + “ “ “ “	200	0
15	“ “ + “ “ “ “	Saline	+++
16	Saline + H serum (ragweed sensitive)	50	+
17	“ + “ “ “ “	100	+
18	“ + “ “ “ “	200	0
19	“ + “ “ “ “	Saline	+++

* J serum A was taken from a non-allergic person before injections of ragweed pollen extract. J serum P was taken after a course of injections of ragweed pollen extract. As the serum did not transfer it had to be mixed with sensitizing serum (H). Normal serum B and saline were used as controls. It took 6 to 8 times as much ragweed to neutralize J serum P as J serum A.

† These mixtures consisted of one part of serum combination (sensitizing and non-sensitizing serum in equal parts) and one part of ragweed extract of designated strength. 0.1 ml. of the serum-ragweed or serum-saline mixture was used for creating each passive transfer site into the skin of a normal test subject.

‡ 0.025 ml. of low ragweed extract (1000 protein nitrogen units per milliliter) was injected into each site.

Cooke, Loveless and Stull: J. Exper. Med. *66*:689, 1937.

Another fact of interest is the short time that this blocking antibody remains in the blood of the infant. In our study we compared the titration

TABLE 10

TRANSMISSION OF BLOCKING ANTIBODY THROUGH THE PLACENTA AS SHOWN BY INACTIVATION OF RAGWEED EXTRACT BY HEATED POST-TREATED SERUMS (CORD AND MATERNAL)*

Dilutions of Heated Serums Mixed with Low Ragweed Extract (10 Protein N Units)	*Reaction of Passive Transfer Sites Prepared with Ragweed Sensitive Serum (Rr. 1:10) and Tested 48 Hours Later With:*					
	Ghl. Cord Serum + Low Ragweed	Ghl. Maternal Serum + Low Ragweed	Aro. Cord Serum + Low Ragweed	Aro. Maternal Serum + Low Ragweed	Bed. Cord Serum + Low Ragweed (Control)	Bed. Maternal Serum + Low Ragweed (Control)
Undiluted	0	0	0	0	++	++
1:3	0	0	0	0	++	++
1:9	0	0	0	0	++	++
1:27	0	0	0	0	++	++
1:81	0	0	0	0	+	+
1:243	0	0	0	0	0	0

---

* Six rows of six sites each were made on the back of a normal test subject by the injection of 0.1 ml. of a ragweed-sensitizing serum (Rr 1:10). The cord and maternal serums were heated at 56° C. for four hours to destroy the skin-sensitizing antibody. To each serum dilution was added an equal amount of low ragweed extract (10 Protein N units). The sites were tested after 48 hours with 0.025 ml. of the serum-ragweed mixtures.

The tabulated results show that even in the undiluted serum-ragweed mixtures the ragweed extract was inactivated by the post-treatment maternal and cord serums whereas in the controls (untreated) a positive reaction was obtained even in the 1:81 dilution. The blocking antibody from the maternal serums Ghl. and Aro. (post-treatment) had passed through the placenta to the fetal blood.

Sherman, Hampton, and Cooke: J. Exper. Med. 72:611, 1940.

TABLE 11

Strict Specificity of Induced Blocking Antibody in a Patient Treated with Ragweed Extract*

Dilutions of Heated Serums Mixed with Pollen Extract (10 Protein N Units)	*Reaction of Passive Transfer Sites Prepared with a Ragweed Sensitizing Serum (Scr. 1:10) and Tested 48 Hours Later With:*					
	Dtch. Serum P. + Low Ragweed	Dtch. Serum P. + Cocklebur	Dtch. Serum P. + Mugwort	Wtsn. Serum A. + Low Ragweed (Control)	Wtsn. Serum A. + Cocklebur (Control)	Wtsn. Serum A. + Mugwort (Control)
Undiluted	0	++	+	++	++	+
1:3	0	++	±	+	++	+
1:9	0	+	±	±	+	+
1:27	0	±	0	0	±	0
1:81	0	0	0	0	0	0

* The technic in this experiment is the same as that described for Table 10. Dtch. Serum P. is a heated post-treatment ragweed reacting serum and Wtsn. Serum, control, is a heated ante-treatment ragweed-sensitizing serum.

This experiment shows that the blocking antibody developed by injections of ragweed extract inactivated ragweed extract only and not cocklebur or mugwort extracts although the patient Dtch. reacted to these extracts. More significant yet, in other passive transfer sites ragweed extract neutralized the skin-sensitizing antibody for both of these extracts as well as ragweed.

Cooke, R. A.: J. Allergy, *15*:212, 1944.

TABLE 12

Inhibition of Low Ragweed Protein Fractions by Serums of Patients Treated With Fraction 1*

Protein Nitrogen Units Per ml.	*Sil. Serum A. (Heated) Plus Fraction 1*	*Sil. Serum P (Heated) Plus Fraction 1*	*Normal Serum (Heated) Plus Fraction 1*	*Sil. Serum A (Heated) Plus Fraction 2*	*Sil. Serum P (Heated) Plus Fraction 2*	*Normal Serum (Heated) Plus Fraction 2*
1	++	±	++	++	++	++
1/3	+	±	++	++	++	++
1/9	+	0	+	+	+	+
1/27	+	0	+	±	±	±
1/81	±	0	±	0	0	0
1/243	0	0	0	0	0	0

* The six rows of six sites each were made on the back of a normal test subject by the injection of 0.1 ml. of a 1:10 dilution of serum from an untreated ragweed hay fever patient.

Serums obtained from a ragweed-sensitive patient Sil. before and after treatment with Fraction 1 were heated 4 hours at 56° C. Mixtures of the heated serums and low ragweed Fractions 1 and 2 were made and diluted to contain the stipulated protein nitrogen unit. The passively sensitized sites were tested after 48 hours with 0.025 ml. of the serum-fraction mixtures.

Note: Results obtained show that Sil. ante-treatment serum did not bind ragweed extract which reacted in 1/81 of a unit, whereas Sil. post-treatment serum bound ragweed so that it reacted only to 1/3 of a unit. When the Sil. serums A and P were mixed with Fraction 2 there was no difference in the reaction between A and P serum, thus indicating that patient Sil. treated with Fraction 1 had developed blocking antibody for Fraction 1 and not for Fraction 2. The reverse of this is shown in Table 13. The specificity of the blocking antibody for a protein fraction of the ragweed pollen is demonstrated.

TABLE 13

Inhibition of Low Ragweed Protein Fractions by Serums of Patients Treated with Fraction 2*

Protein Nitrogen Units Per ml.	*Nez. Serum A (Heated) Plus Fraction 1*	*Nez. Serum P (Heated) Plus Fraction 1*	*Normal Serum (Heated) Plus Fraction 1*	*Nez. Serum A (Heated) Plus Fraction 2*	*Nez. Serum P (Heated) Plus Fraction 2*	*Normal Serum (Heated) Plus Fraction 2*
1	+	+	+	+	±	+
1/3	±	±	+	+	0	+
1/9	±	±	±	±	0	±
1/27	0	0	±	0	0	±
1/81	0	0	0	0	0	0
1/243	0	0	0	0	0	0

* The procedures used in this table are exactly comparable to those indicated in Table 12.

of blocking antibody in cord blood with that in the blood of the same infant after several months of age. The experiments showed that it had practically disappeared six months after birth.

It was shown also that this antibody binds and neutralizes antigen though it does not form a definite precipitate, demonstrable with the usual technics, and finally it appears to have specificity (Table 11) in line with the artificially induced precipitating antibodies as shown in Hektoen-Boor's[6] work. This is quite in contrast with the lack of specificity of the skin-sensitizing antibody previously mentioned.

It is possible to go one step further in emphasizing the specificity. Ragweed extract is, as stated, a mixture of many protein substances.[4, 5] A blocking antibody is specific for each of the protein Fractions 1 and 2. They may be separately titrated and have no part in common (Tables 12 and 13). In other words, following such mixture injections as whole ragweed pollen extract, separate blocking antibodies for several different proteins may be present. Fraction 1 is a good antigen and readily produces its own blocking antibody, while Fraction 2 is not highly antigenic and its blocking antibody is only occasionally demonstrated.*

The blocking antibody, then, is similar to the antibodies artificially produced by other antigens. It is really in the nature of a precipitin for it binds antigen and in the absence of discernible precipitate it resembles the soluble precipitins described by Pappenheimer[18] and by Heidelberger.[19]

From such observations it seems reasonable to conclude that there are certain fundamental differences that have been shown to exist between the blocking antibody produced by pollen protein injections and the naturally occurring skin-sensitizing antibodies, which are as follows:

Characteristic	*Skin-Sensitizing Antibody*	*Blocking Antibody*
Specificity	Relatively non-specific	Relatively specific
Molecular combining groups	Multiple	Single
Cellular affinity	Present	Absent
Antigen affinity (in vitro)	Absent	Present
Heat effect	Labile	Stabile
Placental filtration (cellular affinity or molecular size?)	Absent	Present

Clinical Immunity and the Blocking Antibody

I have spoken of the blocking antibody as an immune body but this is meant only in the sense that it is produced as the result of an immunologic procedure, that is, by pollen protein injections (ragweed extract). The question is, is it really *the* immune body responsible for the clinical protection afforded certain treated hay fever patients? Certain facts compel me to express doubts, especially as evidence is not yet complete.

* This specificity may be more apparent than real, for unpublished work by Sherman indicates that the blocking antibody created in a patient may seem completely specific as shown in passive transfer sites made with sensitive serum X, but appear less specific in sites made with sensitive serum Y. This indicates the complexity of the antigen sensitizing immune system in this type of spontaneous allergy.

It is known from the studies of Hecht et al.,[20] Stull et al.,[4, 5] and Rockwell[21] that extract of whole ragweed pollen contains several proteins. A separate blocking antibody has been demonstrated for both Fraction 1 and Fraction 2. Ample evidence that both fractions are important in causing hay fever is obtained from clinical observations and from the fact that one or both fractions give positive skin and eye tests and systemic reactions in certain persons.

If one assumes the blocking antibody to be an important protective mechanism it is necessary to show that it exists for all fractions of the pollens that react in each individual case, hence no decision can be made until purified fractions of pollen extract are used for skin testing, for treatment and for serum studies of the different specific blocking antibodies.

The orthodox conception of a protective antibody is that a certain amount protects against a certain amount of antigen. There is no basis for individualizing the protective effect of a protective antibody or for assuming that it must vary with each patient rather than for the amount of antigen.

A correlation between clinical improvement in the patient and the titre of immune antibody in the serum is a prerequisite to establishing the claim that the blocking antibody is the essential antibody concerned in clinical protection. The data are difficult to obtain for it must be admitted that an accurate estimate of clinical improvement in hay fever is practically impossible on account of the number of definitely variable factors involved. Gelfand and Frank,[23] Scully and Rackemann[13] found no correlation between the two nor have I in the cases studied in my clinic. Loveless[22, 24] expresses an opposing view.

As I have said, the blocking antibody behaves as a neutralizing or inhibiting antibody of the nature of precipitin. If one adopts the justifiable procedure of reasoning by analogy, precipitation or its counterpart agglutination has not been shown to relate itself quantitatively to the degree of clinical protection in certain bacterial diseases. The third conclusion of Longfellow and Luippold[25] in their studies on typhoid states "No light has been shed on the role of agglutinins in the production of immunity. The discrepancies between agglutinin titres and protective titres brought out in these experiments illustrate once more a potential error in accepting the agglutinin content of a serum as an index to the protective potency of that serum or an index to an individual's immunity."

On the other hand it is possible to show that there exists some kind of a protective mechanism that does not depend upon the presence of any demonstrable blocking antibody. The following case study illustrates this point. The patient, JOH, formerly suffered with ragweed hay fever for which he had never taken treatment. He had had no symptoms for the past eight years though living in a ragweed pollen area. He was exquisitely sensitive to test in skin and eye with an extract of ragweed Fraction 1 and whole extract. His serum showed reaction on passive transfer in a dilution of 1:100. With the usual technic an active ante-treatment skin-sensitizing serum (BRO) was used for neutralization tests. The serum of patient JOH was heated to destroy the skin-sensitizing antibody while leaving the presumed blocking antibody intact. When added to BRO serum no change in the neutralization point resulted (Table 14). This study is a duplication of that recorded in Table 9 where it is shown that J serum P increased the amount of ragweed extract needed to neutralize the skin-sensitizing antibodies in H-serum from 200 units to 1000 units, thus demonstrating blocking antibody. JOH serum did not do this and so contained no blocking antibody to account for his protection.

TABLE 14

Absence of Blocking Antibody in a Symptom-free Ragweed-sensitive Patient (JOH)*

Skin Site on Test Subject	*Serum-Low Ragweed Fraction 1 Mixtures‡*		*Reaction at Site when Tested after 48 Hours with Fraction 1 1/40 ml.–1000 Protein-nitrogen Units per ml.*
	Serum Combinations	Protein Nitrogen Units per ml.	
1.	Bro.† serum + Joh. serum (heated) + Fraction 1	10	+
2.	Bro. serum + Joh. serum (heated) + Fraction 1	30	0
3.	Bro. serum + Joh. serum (heated) + Fraction 1	100	0
4.	Bro. serum + Joh. serum (heated) + saline	Control	+++
	Controls		
5.	Bro. serum + normal serum (heated) + Fraction 1	10	+
6.	Bro. serum + normal serum (heated) + Fraction 1	30	0
7.	Bro. serum + normal serum (heated) + Fraction 1	100	0
8.	Bro. serum + normal serum (heated) + Saline	Control	+++

* JOH serum is from a symptom free patient exquisitely skin and eye sensitive to protein Fraction 1 and to whole ragweed extract but not to protein Fraction 2. Passive transfer dilution tests (not recorded here) were positive up to 1–100. The heated serum was unreactive in full strength.

†Bro. serum is an ante-treatment sensitizing serum from a ragweed hay fever patient.

‡ These mixtures consisted of one part of serum combination (sensitizing and non-sensitizing in equal parts) and one part of Fraction 1 extract of designated strength. 0.1 ml. of the serum-fraction mixtures or serum saline mixtures was used for creating each passive transfer site in the skin of a normal test subject.

From this observation it must be deduced that patient JOH had some mechanism to offset his demonstrable sensitization, and that the pro-

TABLE 15

EFFECTS OF RAGWEED POLLEN INJECTIONS ON PATIENTS SENSITIVE TO CERTAIN FRACTIONS OF RAGWEED POLLEN

Case	*Reaction of Passive Transfer Sites Tested with*		*Neutralizing Antibody Developed for:*		*Highest Dose**	*Constitutional Reactions*	*Clinical Improvement*
	Fraction 1	Fraction 2	Fraction 1	Fraction 2			
1	++	0	+	0	6000	0	90%
2	++	0	+	0	2000	0	Marked
3	++	0	+	0	1500	0	80%
4	++	0	+	0	8000	0	95%
5	++	0	+	0	5500	0	75%
6	++	0	+	0	10,000	0	50%
					Av. 5300		
7	++	±	+	0	1000	1	90%
8	++	+	+	0	2000	2	75%
9	++	+	+	0	700	1	Marked
10	++	+	+	0	1250	0	Fair
11	++	++	+	0	2000	2	90%
12	++	++	+	0	1250	0	75%
					Av. 1360		
13	++	++	+	+	7500	0	98%

* Protein nitrogen units of whole ragweed extract.
Sherman, W. B.: J. Immunol., *40*:289, 1941.

tective mechanism was not the blocking antibody. This experiment indicates a protective factor or at least some means of protection at present unknown and unsurmised.

However, there is evidence that the blocking antibody has some beneficial effect. The data presented in Table 15 show that treated ragweed hay fever Cases 1–6 were reactive only to Fraction 1 with blocking antibody for this fraction. They took doses averaging over 5000 protein nitrogen units of whole ragweed extract without systemic reactions, whereas Cases 7–12 reacting to both Fraction 1 and Fraction 2, but with antibody only to Fraction 1, were able to take doses averaging less than 1500 units, and with a total of six systemic reactions. Case 13, reactive to and with blocking antibody to both fractions, took doses up to 7500 units with no reaction. One interpretation of these results would be that the presence of the blocking antibody permits increasing dosage without the danger of the constitutional reactions at a level well above that where no such antibody is found, but the antibody must exist for all those fractions of pollen to which the patient is reactive. For example, the group of patients 7–12 are reactive to Fractions 1 and 2, but have no blocking antibody for Fraction 2, hence cannot take amounts of ragweed extract containing both fractions without systemic reactions. The doses must be held down. In contrast is Case 13 with antibody for both fractions who was given dosage to 7500 units without difficulty.[3]

Summary. I have tried to give an unbiased appraisal of the functions of the blocking antibody. Possibly it is a factor in clinical immunity but in view of what has been said I do not think there is yet sufficient proof that it is the most important factor. However, from the studies presented there is an indication that it has a beneficial effect against an increasing dosage of ragweed extract. Evidence has been submitted to show that there is some other unknown mechanism of immunity which operates in the complete absence of demonstrable blocking antibody. The factors in hay fever immunity deserve continued study.

These serologic studies on the skin-sensitizing and the immune or blocking antibody do not at present offer much practical help, but they tend to throw light on the intricacies of the sensitization phemonena in one type of allergy dependent upon skin-sensitizing antibodies and disclose the co-existence of a sensitized and immune state at one and the same time. Sensitization and immunity are not identical in so far as these studies can show.

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4. *Pathologic-Anatomic Aspects of Allergy*

PAUL KLEMPERER

Allergy is a dynamic concept. It manifests itself in functional aberrations which are revealed by clinical symptomatology, physiologic, pharmacologic and chemical investigations, and, above all, by immunologic and serologic tests. It might be expected that the altered reactivity of the body would be associated with definite structural alterations of organs and tissues and that, accordingly, we should be able to present a concise picture of the pathologic anatomy of allergic conditions. Yet, while extensive and intensive morphologic investigations have been carried on since the discovery of allergic states, it has not yet been possible to establish criteria which would allow us to diagnose the existence of an allergic state from the anatomic-histologic picture alone.

There are several reasons for this failure, some of which will be discussed later. The main difficulty confronting the histologic diagnosis of allergy in human disease is the complexity of the process in bacterial infections, the course of which is so fundamentally influenced by allergy. In order to analyze the structural lesions in these complex morbid states, it is necessary to become familiar with the morphologic alterations observed in the simplest and best understood forms of allergy. Consequently, I shall discuss first the pathologic anatomy in general and local protein anaphylaxis in the experimental animal and in the human being.

Pathologic Anatomy in Anaphylaxis

General. The gross and microscopic anatomic picture of general anaphylaxis is dominated by certain organ alterations which are the result of *functional hyperactivity of smooth musculature*, without obvious tissue damage. Expansion of the lungs due to spasm of the smooth musculature of the bronchi is the reaction in the guinea pig, distention of the right ventricle due to spasm of the pulmonary arteries in the rabbit, congestion of the liver and alimentary tract due to spasm of the muscle cushions of the hepatic veins in the dog. While not many necropsy observations are available of general anaphylactic shock in the human being, the report of Vance and Schlossman[1] indicates the occurrence of bronchial spasm with distention of the lungs. Hyper-reactivity of the smooth muscle is one of the fundamental functional alterations of the allergic body and need not be associated with any obvious morphologic lesion. The uterus of the allergic guinea pig, which reacts so promptly in the Schultz-Dale experiment, shows no morphologic lesions. It is then understandable that in a variety of human allergic conditions characterized by muscular spasm, morphologic examination does not disclose any alteration.

Local. In contrast to the lack of conspicuous morphologic alterations in general anaphylaxis, local tissue anaphylaxis is characterized by the most profound structural lesions. In fact it was the conspicuous macroscopic alteration of the skin after repeated reinjection of foreign protein which led to the discovery of the principle of tissue hypersensitivity, as expressed in the Arthus phenomenon. Since then many histologic investigations have been carried out and the development of the lesions has been studied in great detail (Figs. 3 and 4).

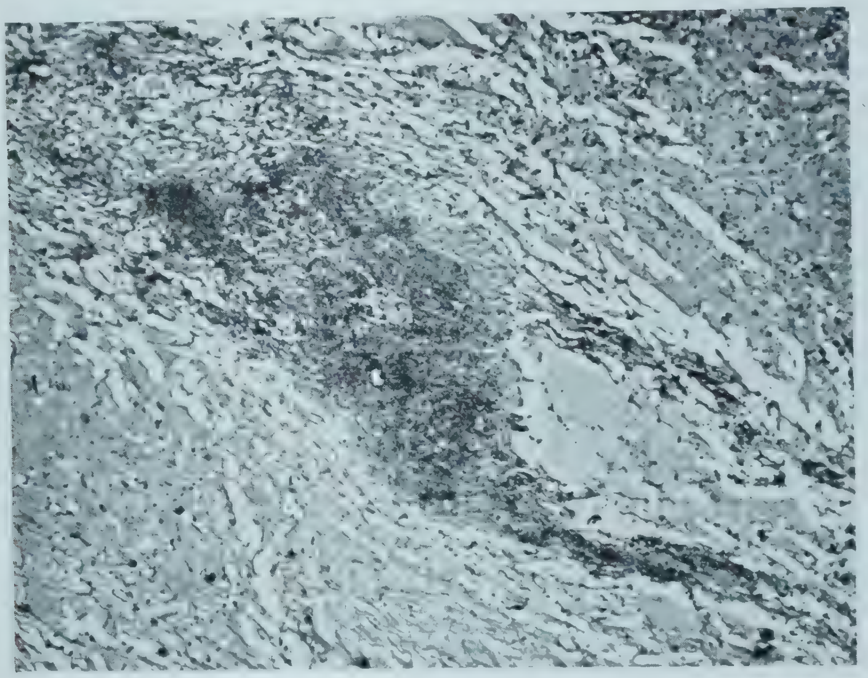

Fig. 3.—Skin of rabbit injected subcutaneously three times with 1 ml. horse serum, at four-day intervals, twenty-four hours after last injection. Edema of cutis and fibrinoid degeneration of collagen fibers.

There is general agreement that the sensitized rabbit reacts with severe *inflammation* to the reinjection of a small amount of protein, while the unprepared animal shows no response to the injection of a similar or even larger dose. The quality of the inflammation, however, is not characteristic, i.e., it does not differ fundamentally from the inflammation elicited by the injection of a variety of toxic substances or upon physical irritation, although the conspicuous edema and the fibrinoid collagen degeneration are generally not so striking in ordinary inflammation.

While the skin of the back or of the abdomen of the rabbit shows, generally, this picture, the process does not develop to the same degree of necrosis in the ear of the rabbit. However, the inflammatory character of the lesion is very evident. In addition, the epidermis of the ear shows peculiar eczematous changes which persist over a long period and are not so evident in other parts of the body surface. The Arthus phenomenon is best seen in the rabbit but it can be elicited in other animals too, as has been shown by Gerlach. The intensity of the inflammatory reaction varies in different animal species. It can be produced in the human skin and accidents during serotherapy have testified to it. It has been studied histologically by Gerlach[2] who used his own skin for the experiment. If the hyperergic inflammation in the Arthus phenomenon is the typical reaction of the protein-sensitized animal body, one can expect that an identical reaction can be provoked in the skin of the idiosyncratic individual if injected with the sensitizing allergen. Berger and Lang[3] have carried out histologic investigations in such cases and have indeed been able to show that similar pictures can be produced both in actively sensitive individuals and in the skin of normal man locally sensitized by passive transfer. The presence of eosinophile polymorphonuclear leukocytes has been stressed as illustrated on plate I of their report.

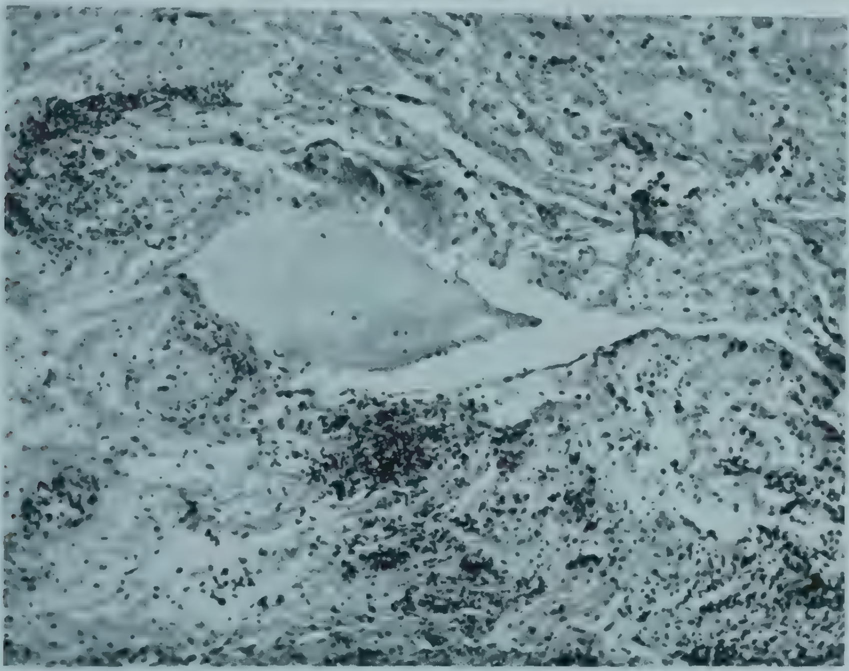

Fig. 4.—Skin of rabbit injected subcutaneously three times with 1 ml. horse serum, at four-day intervals, forty-eight hours after last injection. Edema and infiltration of cutis with polymorphonuclear leukocytes.

If a hyperergic inflammation is the reaction of the skin of the sensitized animal, one must ask how other organs of such an animal react upon the reinjection of the specific allergen. A considerable number of experiments have been carried out to clarify this point (Seegal, D., Seegal, B. C., and Jost, E. L.[4]). Practically every site in the rabbit has been tested and these investigations have shown that the same type of reaction can be elicited in any part of the animal body by direct injection of the antigen. Inasmuch as inflammation is a process in which primarily the connective tissue-vascular system is involved, one may conclude that this system, the mesenchyme of the body, is sensitized, or in other words, is a shock organ.

Attempts have been made to visualize the evolution of the process leading to the complex tissue damage evident in the Arthus phenomenon. In the mesentery of the sensitized frog and in mammals in which the process within the peritoneal cavity has been observed through a window, it has been shown that the hyperergic inflammation begins with an alteration of the blood circulation. Consequently the vessel wall, and especially the endothelium, has been considered as the primary site of the reaction. However, Fröhlich[5] and particularly Ricker and his school[6] have ventured the opinion that the circulatory disturbance is mediated by the nerves and expressed the belief that the vasoconstrictors are the first point of attack of the antibody-antigen reaction supposed to occur in the reinjected sensitized animal. Morphologic investigations have so far not been able to clarify this point and we must be satisfied with the conclusion that as far as morphologic studies indicate, the connective tissue-vascular system in its totality is implicated in the phenomenon of local anaphylaxis.

If the totality of the implication of this system is emphasized, it is because we can see alterations of all its constituent elements, the blood vessels, the connective tissue fibers and ground-substance, and the cells. Of the last it is not only the emigrated blood cells which are conspicuous, but also the fixed elements, the fibroblasts and especially the histiocytes, show striking proliferation, especially in later phases but also in early stages of the reaction if the amount of injected antigen is decreased. It is the proliferation of the histiocytes which leads to an encapsulation of the injected antigen, as the experiments of Rössle[7] on the rabbit, sensitized with chicken erythrocytes, have shown. In these experiments as well as in those of Roulet,[8] the proliferating histiocytes form small nodules, granulomata, around the injected antigen, similar to the foreign body granuloma. Thus we can add the histiocytic granuloma to the histologic phenomena of the experimental allergic tissue reaction. It has been maintained by Dienes and Mallory[9] that histiocytic proliferation is the main tissue response in the tuberculin type of hypersensitivity.

I have mentioned before that the skin is the most convenient site to provoke and demonstrate local tissue anaphylaxis, but it can be elicited in any part of the body upon direct reinjection of the sensitizing allergen. In other words the mesenchyme of the entire body becomes sensitized. It cannot be surprising, therefore, that reactions may occur in the proximity of the site of injection or even at greater distance if part of the injected antigen is resorbed into the lymph or blood stream. However, because small amounts only are resorbed due to the protective action of the local hypersensitivity reaction, the distant tissue changes are generally only slight or reveal a part only of the full blown hyperergic inflammation. Thus Klinge,[10] by injecting horse serum into the joint cavities of sensitized rabbits, produced a necrotizing arthritis and found also foci of collagen degeneration and histiocytic granulomata within the connective tissue septa of the myocardium.

Tissue Alterations Produced by Antigen. A great number of investigations have been carried out to study the tissue alterations resulting from the repeated injection of antigen into the blood stream. The results vary depending on the amount and the primary toxicity of the injected antigen. With the injection of *small* amounts of horse serum into the rabbit's blood, Epstein[11] saw a striking proliferation of basophilic histiocytes within spleen and liver, which he considered as the morphologic evidence of immunity. Siegmund[12] and Dietrich[13] saw similar cell proliferations after the injection of killed coli bacteria, associated with proliferation of endothelial cells of hepatic veins and of the valvular endocardium. Upon reinjection of living bacilli, the endothelial proliferation became prolific leading to small venous cell thrombi and verrucae upon the endocardium. The proliferated endothelial cells contained phagocyted bacteria and because the animals survived the injection of amounts of living bacilli lethal for normal animals, the authors concluded that the cellular proliferation was the morphologic expression of immunity. It must be mentioned, however, that similar endothelial activation including the formation of venous thrombi can be produced by a single intravascular injection of bacterial toxins as Apitz[14] and Gerber[15] have shown.

The intravenous injection of *large* amounts of antigen into the sensitized animal leads to far more dramatic tissue changes. Klinge and Vaubel[16] have carried out such experiments with horse serum and produced severe cardiac and especially vascular alterations. Rich and Gregory[17] recently reported the production of generalized necrotizing arteritis simulating periarteritis nodosa in man upon the single intravenous injection of very large amounts of horse serum into rabbits, thus providing the opportunity for a protracted circulation of antigen while hypersensitivity develops.

From all these experiments in which primarily nontoxic antigens were used—the anaphylactic type of hypersensitivity—one must conclude that severe tissue alterations result from the interaction of antigen and antibody in the living animal. If it is asked, however, whether these tissue lesions are specific for the allergic response of the living body, the answer must be in the negative. Both the inflammatory reaction with cell emigration and cell proliferation, and the fibrinoid collagen degeneration, can be provoked by physical or chemical agents, not to speak of the direct action of bacteria or their toxins. Only the eosinophilic response seems so far to be more specific, but it must be mentioned that this is often missing. It is evident then that even in the relatively simple experimental anaphylactic or Arthus phenomenon type of hypersensitivity, the tissue lesions are not of diagnostic value. In other words, the microscope does not reveal the allergic mechanisms of the structural alterations; at best it is only suggestive. How much more complicated is the situation in the type of hypersensitivity which develops in the course of infections with living microorganisms, not to speak of viruses.

Allergic Hypersensitivity and Infection. While the essential points of immunologic dissimilarity between the anaphylactic and the tuberculin type of hypersensitivity have been well recognized since Zinsser's early contribution, differences in the tissue reaction have not yet been so well recognized. Dienes and Mallory,[9] in their elaborate experiments using animals with mild allergic reactions, established certain histologic differential points between the anaphylactic and the tuberculin type of hypersensitiveness. The difference, however, is not evident in strong reactions and consequently it has not been considered very seriously by morphologists.* In fact, many pathologists, especially the German school of Klinge and Rössle, have drawn conclusions as to the allergic nature of certain diseases, such as rheumatic fever, from an apparent similarity between the structural alterations in this morbid condition and those of the experimental animal in the anaphylactic type of hypersensitiveness. But even if one would disregard the possible dissimilarity of the tissue reaction in both forms of hypersensitivity, the complexity of the factors in infections would make an analysis of the histologic picture with reference to the part played by allergy most difficult.

Some of the main factors which enter into infections and cause tissue reactions identical or very similar to those of allergy might be mentioned. The primary toxicity of the micro-organisms or their toxins, their ability to multiply within the body, the effect of the Shwartzman phenomenon elicited by the products of the micro-organism, not to speak of the interference with the metabolism of the host by the life activity of the invading micro-organisms, most probably evoke a multiplicity of tissue changes which so far withstand any attempt at analysis. We are, therefore, on firm ground only if we limit our attempts to evaluate the role of allergy in the pathologic anatomy of human disease to such morbid states in which the exact investigation of the living patient leaves no doubt as to the fundamental importance of the allergic factor. Necropsy observations in these truly allergic diseases are not frequent.

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* Follis,[18] in a recent publication, could not confirm their observations.

The Role of Allergy in Disease

Bronchial Asthma. The gross anatomy of bronchial asthma shows only the result of the spasm of the small bronchioles which leads to an extreme degree of emphysema. This alone cannot be considered as characteristic of an allergic mechanism because similar degrees of emphysema can be found in patients suffering from bronchiolar occlusions due to other causes. The histological examination, however, reveals a picture which can be considered as characteristic (Figs. 5 and 6). Although there is not much need to support the allergic mechanism of bronchial asthma by experiment, it is interesting to mention that identical morphological changes were observed by Pagel and Kallos[19] in the sensitized guinea pig, in which asthmatic attacks have been produced by the insufflation into the trachea of the specific allergen.

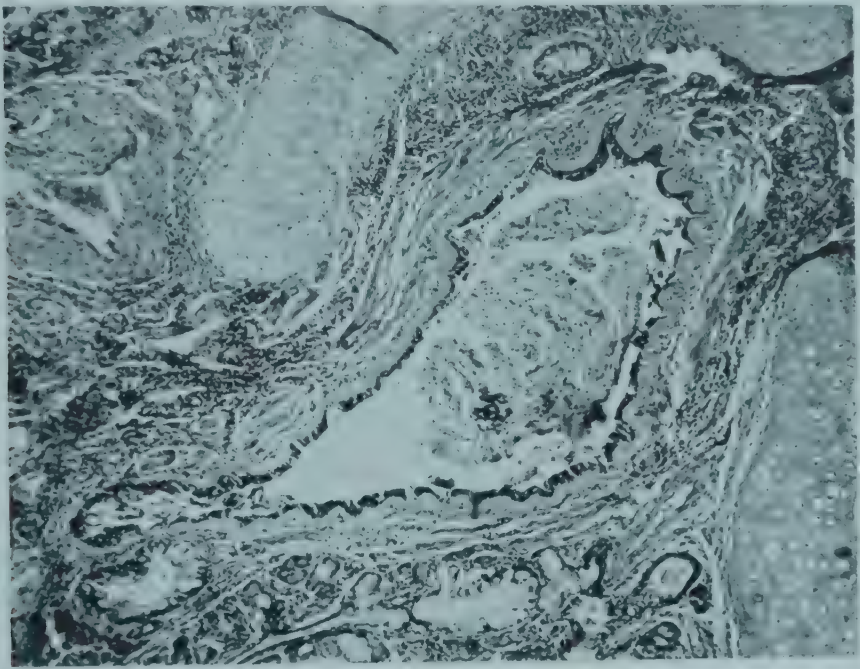

Fig. 5.—Bronchiole in case of bronchial asthma. Lumen filled with mucus inclosing a few eosinophile polymorphonuclear leukocytes. Hyalinization of basement membrane. Hypertrophy of circular smooth musculature.

If we evaluate the tissue changes in bronchial asthma, we must concede that the eosinophilia alone suggests the existence of an allergic state. But it is interesting that, while attacks of asthma simulating that of bronchial asthma can be provoked in the normal guinea pig by the introduction of histamine into the trachea, the tissue reactions in such animals lack the presence of eosinophile leukocytes, and the other features of human bronchial asthma, such as hypersecretion of mucus, hyalinization of the basement membrane and hypertrophy of the bronchial musculature, are also generally absent or negligible.

Serum Sickness. The opportunity to observe cases of serum sickness at the autopsy table has not been frequent, particularly cases which can be considered as purely due to the influence of the foreign protein.

A number of cases have been reported in recent years by Clark and Kaplan,[20] and by Rich,[21] of instances of delayed death following treatment with antitoxic horse serum, mainly in pneumonia. Among the anatomical observations the most conspicuous were mural endocarditis and myocarditis as well as vascular changes resembling those of periarteritis nodosa. The fact that similar lesions have been produced in animals by the repeated injection of horse serum permits the conclusion that the lesions in the human are also the result of altered tissue reactivity. There seems, therefore, no doubt that the morphological changes in truly allergic diseases are identical with those observed in the allergic animal body.

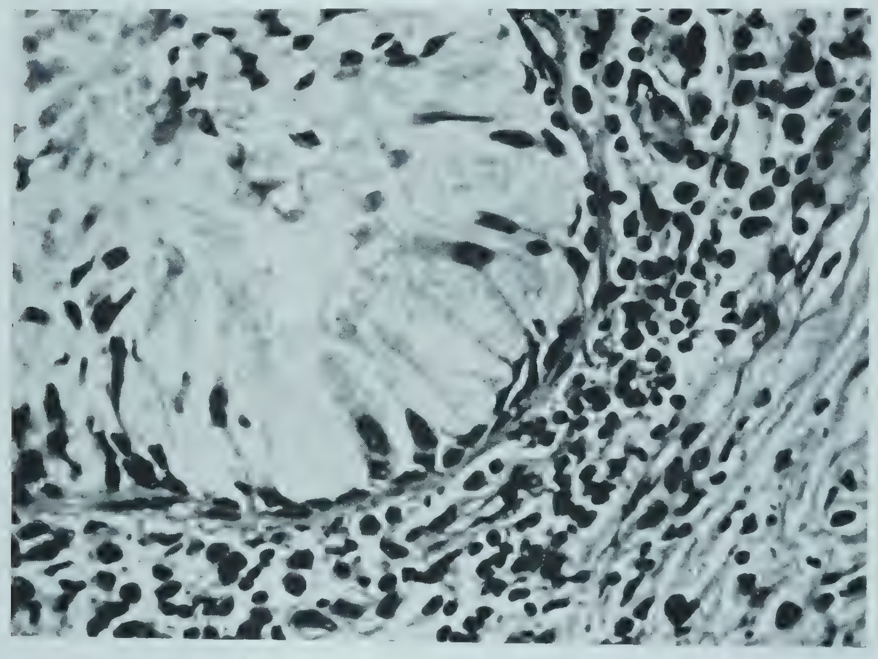

Fig. 6.—High-power photograph of bronchial wall in bronchial asthma. Epithelial cells distended by mucus, infiltration with many eosinophile polymorphonuclear leukocytes.

In approaching the problem of how far morphologic investigations can directly contribute in the elucidation of the significance of allergy in the pathogenesis of human disease, I should like to limit myself mainly to periarteritis nodosa, rheumatic fever and glomerulonephritis.

Periarteritis Nodosa. It was a pathologist, George B. Gruber,[22] who was impressed by the incongruity of the severity of the arterial lesion and the absence of a causative agent. This and the eosinophilia of the perivascular infiltrate led him to the hypothesis that the characteristic necrotizing arteritis could be regarded as an allergic (hyperergic) inflammation of the vessel wall. Clinical observations, such as blood eosinophilia and the relative frequency of a history of asthma, were in support of such a concept. Experiments seem to corroborate the idea. The recent reports of Rich[17, 21] on serum sickness, and his latest experiments, seem to leave no doubt as to the correctness of the theory. Yet I believe a word of caution should be sounded. Not every necrotizing arteritis is necessarily a periarteritis nodosa. We should try to limit the diagnosis to such cases in which all the classical criteria are present. I think Karsner[23] correctly demands that in the diagnosis of periarteritis nodosa "the local eosinophilia should be given a place of great importance." I do not propose to enter into a detailed argument as to the morphogenesis of periarteritis, but I believe that the diagnosis in the strict sense is sometimes not justified and that the term periarteritis nodosa embraces somewhat dissimilar morbid conditions. With this reservation I fully accept the allergic nature of periarteritis nodosa.

Rheumatic Fever. The allergic theory of acute articular rheumatism was first advanced by Menzer in 1902. He accounted for the inflammation as the result of the union of antibodies with streptococci in the tissues. Friedberger produced arthritis by the injection of horse serum into the joint of sensitized animals. Weintraud, impressed by the polyarthritis in serum sickness which was already recognized to be anaphylactic in nature, advanced the hypothesis that rheumatic fever was an anaphylactic reaction to bacterial proteins.

Swift and his collaborators have consistently maintained that rheumatic fever is the result of allergy to a non-hemolytic streptococcus and have supported their contention by a series of carefully conducted clinical, immunologic, experimental and histologic investigations.

Pathologic anatomists were rather slow in showing interest in the hypothesis mainly because Aschoff believed in the specific nature of the rheumatic tissue lesions. Klinge and his school and Rössle have been so much impressed by the morphologic similarity of what they consider the crucial lesions in rheumatic fever and connective tissue alterations in hypersensitive rabbits that they have fully accepted the allergic etiology of rheumatic fever.

It was particularly the fibrinoid degeneration of the collagen tissue found in the disease as well as experimentally which caused Klinge to formulate his concept of the allergic nature of rheumatic fever. It seems, however, that this concept should be supported by more than this morphological evidence, because fibrinoid degeneration of the collagen is certainly not found exclusively under conditions of altered tissue reactivity. Aschoff has consistently maintained that the basic characteristic morphologic feature of rheumatic fever is the rheumatic myocardial nodule. However, these granulomatous formations are found only within the interstices of the myocardium, in the valves and in the pericardium.

while fibrinoid degeneration associated with diffuse cell proliferation characterizes the rheumatic lesions in the auricle and in the vessels. Accordingly, Klinge maintained that the early lesions of rheumatic fever need not show the fully developed Aschoff nodule. He believed that the rheumatic nodule is merely a phase in the development of the characteristic rheumatic tissue lesion. The presence of cellular reaction around foci of fibrinoid collagen degeneration in allergic animals was considered by him as an equivalent to the true Aschoff body.

Aschoff, however, supported by most pathologists, has contended that the lesions of the experimental animal only faintly resemble the rheumatic nodule of the human and should not be identified with it. Aschoff and his school believe that this characteristic lesion is due to an unknown virus and strenuously object to the concept of Klinge. It seems, therefore, that morphologic investigations have not yet fully proved the theory of the allergic nature of rheumatic fever.

However, in the recent article of A. R. Rich and John E. Gregory[26] the similarity of the experimental cardiac lesions with the Aschoff bodies of the human rheumatic heart is convincingly illustrated by the authors. These observations leave, in my opinion, no doubt that lesions, morphologically identical with those found in the heart of rheumatic fever patients, can be produced by an allergic mechanism.

Glomerulonephritis. The fact that glomerulonephritis in the wake of scarlet fever generally begins at a definite period after the acute exanthema was considered by Escherich and Schick as suggestive of the allergic nature of this disease.

Many experiments have been undertaken to reproduce in the animal lesions identical with that of human glomerulonephritis by invoking the allergic mechanism. It is not possible to enter into a discussion of all these ingenious experiments, but it must be stated, however, that so far there is no clear-cut evidence that glomerulonephritis as found in the human can be produced in the experimental animals. Masugi and his collaborators have come nearest to satisfactory results; however, other investigators, using the same technic, have not been able to obtain similar results. The interpretation of the characteristic glomerular anemia in acute glomerulonephritis as the result of a spasm of the afferent arteriole due to allergy is highly speculative. Again we must confess that the allergic nature of this disease, so strongly suggested by clinical investigators, cannot be fully supported by morphologic investigations.

Other Conditions. In presenting the facts offered by morphologic investigations in support of the allergic nature of certain diseases, I have selected those morbid states in which there is undoubtedly a great deal of support of this view to be found from the morphologic examination in association with experimental pathology. It should be made clear that there still remain certain doubts as to the correctness of such a concept.

The morphologic facts alone cannot be considered as conclusive. How much more does this doubt obtain in a great variety of other conditions, such as *thromboangiitis obliterans*, *acute lupus erythematosus*, *scleroderma*, *interstitial nephritis*, *malignant nephrosclerosis*—all conditions in which an allergic mechanism has been considered as fundamental mainly because of certain histologic findings, especially the presence of fibrinoid degeneration of the collagen tissues.

Among these maladies, acute lupus erythematosus shows certainly the most striking degree of fibrinoid degeneration of the connective tissue. In fact, because of the prominence of this tissue alteration, acute lupus erythematosus has been designated a systemic collagen disease (Klemperer, Pollack, and Baehr[24]). Clinicians have often maintained—on rather meager grounds, it seems to me—that disseminated lupus erythematosus is an allergic disease. In investigating the histories of our cases we were unable to find any frank clinical evidence to support such a view. It is true that these cases show frequently sensitivity of the skin to sunlight. However, this type of sensitivity must certainly not be considered as allergic in the strict definition of the word. Altered reactivity against sunlight might fall into the wide concept of pathergy as defined by Rössle.[25] but should not be identified with specific allergy to foreign protein or bacterial allergy. Moreover, the fact of the peculiar sex limitation of this disease permits one to doubt that an infectious allergic factor plays a significant role. To base the hypothesis solely upon the conspicuous and characteristic alteration of the collagen in this disease seems to me narrow and not conducive to further progress.

While it cannot be doubted that fibrinoid degeneration is a characteristic of the allergic state, it should not be maintained, however, that fibrinoid degeneration is equivalent to allergic tissue reactivity. Even the most enthusiastic believers in the role of allergy in human disease, such as Klinge and Rössle, have strenuously opposed such conclusions. It seems to me that pathologic anatomy must be extremely cautious in the evaluation of tissue lesions in reference to etiology. The pathologist must be exact in his investigations and first establish all the facts which the microscope can reveal. He must try to correlate these facts with the facts established by the clinician. Experiments must guide him before he accepts a cause-and-effect relationship between an etiology suggested by observations in the living and tissue alterations found at the autopsy table. The findings in the dead can only support conclusions reached by observations on the living.

Allergy is a dynamic process which provokes certain tissue changes, which in themselves are not characteristic. To try to prove existence of a dynamic process from purely morphologic observations must lead to sterile speculation.

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5. *Immuno-Chemistry of Antigens and Antibodies*

MICHAEL HEIDELBERGER

THE narrow point of view of the chemist makes possible a tremendous oversimplification of the problems about to be discussed. The very complex phenomena that are grouped together under the name of immunity and allergy will be considered as the interplay of antigens and antibodies. This leaves out the entire clinical side as well as the physiology and pharmacology of these states.

Antigens

Complex Nature of Antigens. "Horse serum was used as an antigen," or "typhoid or tubercle bacilli were used as antigens," or "pollen was used as an antigen," are misleading expressions because practically all of the natural antigens are mixtures. It has been mentioned previously that there is more than one reactive substance in pollens, and serum is a complex mixture also, as are the cells of pathogenic microorganisms.

This may be verified by looking at horse serum through the eyes of the Tiselius apparatus. This is an electrophoresis cell which takes advantage of the electric charges of proteins and is designed to give not only the maximum separation at different hydrogen ion concentrations, but to record the separation through an optical system based on differences of index of refraction. One gets a peak for each component separated. Wherever there is a boundary, there is a maximum difference in the index of refraction, as at the advancing boundary of a protein moving under the influence of the electric field into a salt or buffer solution, and this is translated by the apparatus into a peak characteristic for the protein component.

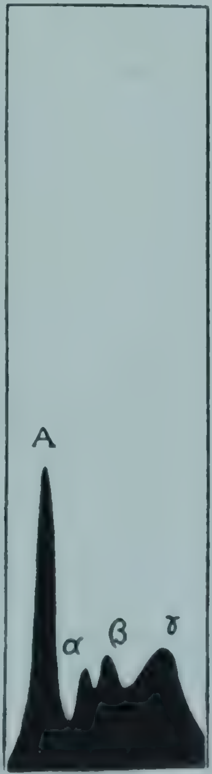
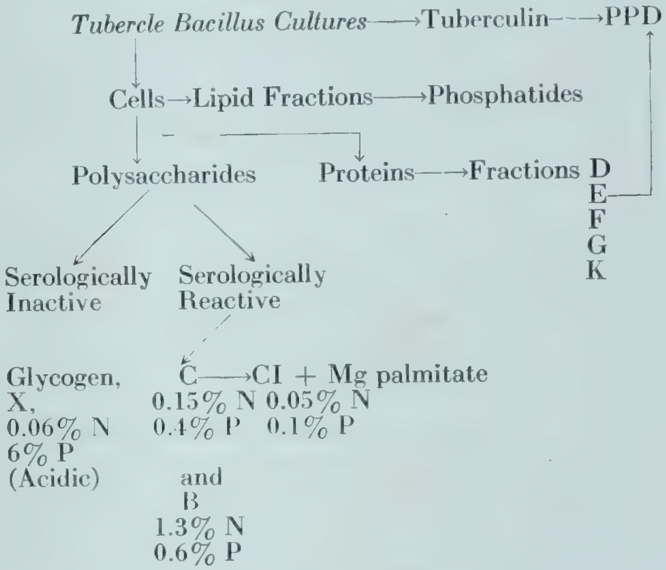


Fig. 7.—Horse serum in the Tiselius apparatus.

In serum there are at least four peaks, indicating that there are at least four components: the well-known albumin, and what Tiselius called alpha, beta and gamma globulins. The division into euglobulin and pseudoglobulin is not made in this case, because some of the water-insoluble globulins appear in almost every one of these fractions. These fractions are based upon their difference of electrical charge at the hydrogen ion concentration and in the buffer used (Fig. 7).

Abramson et al.[1] in their work on the electrophoresis of ragweed pollen found a major colorless component which seemed to make up the principal portion of the soluble material, and then there were a number of minor, highly pigmented components. Almost any natural antigen would give a picture rather similar to this in which the proportions of the components and their mobilities would be different, depending upon the electric charge characteristic of the protein in question.



The accompanying diagram illustrates some of the varied products that have been isolated from the tubercle bacillus to show the antigenic complexity of a single strain of bacillus. This is a human strain (H-37), and with it, of course, tuberculin, a very powerful antigen, is given off into the culture medium. From this, Seibert has separated the purified protein derivative, PPD, which elicits reactions in very high dilution in sensitive persons.

In the cells there are very large lipid fractions, and characteristic of these are not only the phosphatides, but a tremendous variety of other substances which Anderson[2] has described in great detail, but which need not be discussed here. In the cells are also a number of proteins which are more strongly antigenic when injected into animals than the tuberculin proteins, and probably represent less degraded protein. It was possible to separate several fractions with different properties and of these at least two were immunologically distinct. The others were perhaps mixtures of these two, and perhaps represented still other products, so there are at least three proteins, in addition to the lipid fractions, of of which the phosphatide is also supposed to have immunological properties.

In addition there are a large number of polysaccharides. These are separable into a serologically inactive group, consisting of glycogen and an unknown acidic phosphorus-containing polysaccharide, and a whole group of polysaccharides reactive in antiserums to the tubercle bacillus, giving specific precipitates. These were separable into two of entirely different specificity. The antibodies to one could be absorbed out without removing the antibodies to the other, and one of the polysaccharides could be degraded into magnesium palmitate and an additional serologically reactive artifact which apparently did not exist in that form in the original cell. So if the polysaccharides are included among the antigens there is an enormous complexity and at least five or six immunologically reactive substances in the tubercle bacillus cell. More could probably be found if methods of separating and testing were more sensitive.

Chemical Structure of Antigen. *The Protein Molecule.* It is obvious that many antigens are proteins and that most proteins are antigens, but this does not explain why they are antigens. Modern chemistry and physics, however, have disclosed some facts about the protein molecule which may help to solve this problem.

It is well known that the fundamental protein structure consists of polypeptide chains united into what Wrinch[3] calls fabrics; at any rate there is a terminal amino group to each chain, and that is in the position next to the carboxyl of the terminal amino acid, and this carboxyl is linked in amide-linkage to the amino group of another amino acid and so on. For example serine, $HOCH_2CH(NH_2)COOH$, is linked in the same way to another amino acid, or the same amino acid. We may put in phenylalanine, $C_6H_5CH_2CH(NH_2)COOH$, also and that may be linked to another acid, or the same one. Lysine, which has an extra amino group on the end of it, may be added and so on, more or less *ad infinitum*, to build up a polypeptide chain, $RCH(NH_2)CONHCHR'CONHCHR''$ . . .

The polypeptide chains are not just straight chains; they are probably coiled up and looped back upon each other, and there is a great deal of evidence now, brought forward partly by x-ray examination and partly by Pauling[4] on the basis of the physical-chemical behavior of proteins, that many of these chains are held together by hydrogen bonds which form through the hydroxyl groups of the hydroxyamino acids such as serine and threonine.

There is a very high percentage of these hydroxy amino acids in proteins, much higher than was thought originally (Brand[5]). They seem to exercise the important function of holding the huge chains together into a single large molecule through these auxiliary bonds, which are called hydrogen bonds, and which are particularly characteristic for the hydroxyl groups and the SH groups. Cysteine, too, may function in much the same way.

In most proteins there is either a surplus of amino groups, in which case the protein is a basic protein, or there is a surplus of carboxyl groups due to a high content of glutamic acid or aspartic acid, and the protein is an acid protein, or it may be neutral like hemoglobin and have an iso-electric point, or point of minimum electric charge, very close to neutrality.

SHAPE. The way that these chains are held together determines the shape of the large protein molecules. There are very few whole proteins known that have a molecular weight of less than about 35,000, and many proteins may weigh many millions, such as the hemocyanins, the respiratory pigments of snails, and the viruses.

The earlier views on the structure of the protein molecule assumed that it was spherical in shape, simply because this was the easiest way to pack a vast number of peptide chains into a compact form. By x-ray analysis and through the use of the ultracentrifuge, which whirls proteins out of solution at very high gravitational forces, and by methods of diffusion which give some inkling as to their shape when combined with the rate at which the centrifuge throws them out of solution, one can derive mathematical formulas with the aid of certain assumptions. By these assumptions the conclusion has been reached that very few proteins are actually spherical, but that they have varying shapes.

For instance, some proteins may be disk-shaped. Others, such as the tobacco mosaic virus—the molecule of which has actually been seen in the electron microscope—are long, narrow rods, and the dimensions can be measured. There is reason to think that other proteins are more or less oval, or cigar-shaped, and that perhaps is the most common shape of the protein molecule, presumably with many local irregularities. The bacteriophage of Bacterium coli resembles a spermatozoon under the electron microscope, and it seems to be a highly specialized protein molecule with a molecular weight up in the millions.

CRITERIA OF ANTIGENICITY. It is apparent that shape alone is not sufficient for antigenicity. When one goes back over all the structural evidence, there seem to be two more or less necessary criteria for antigenicity: one, that the molecule be large, and two, that there be the opportunity for the repetition on the reactive surface of the molecule of certain characteristic or critical groupings. If two like portions of polypeptide chains emerge on the reactive surface of the protein and then go back into the interior of the molecule again there will be two similar areas on the protein surface. It is quite possible from what is known of the numbers of amino acid groups—there are often sixty or seventy or one hundred glycine or alanine or eight to twenty tyrosine residues in a single protein molecule—that two or three or six or twenty similar molecular groups could emerge on the surface X times, and then there would be a chemical or immunologic *multivalence*. For our purpose, chemical and immunologic valences mean the same thing, that is, if one has more than one of the same kind of grouping, one has what the chemists call a multivalent substance, and that substance can engage in immune reactions, as will be seen later.

Polysaccharides as Antigens. Some years ago in Avery's laboratory a new group of substances concerned with the type-specific immunologic reactions of penumococci were found, which turned out to be polysaccharides. They were a strange group of sugar derivatives which were not affected by the usual ferments that split starch and cellulose and other ordinary polysaccharides. They seemed extremely resistant, and they had the same property that proteins have, of precipitating antibodies, formed when the bacterial cells from which these sugar derivatives were derived were injected intravenously into animals.

In Table 16 are given the chief physical and chemical constants of the type-specific substances of Types I, II, III, IV and VIII pneumococcus. As is seen, the deviation of the plane of polarized light characteristic for each one of these sugar derivatives is very different from that of the others. The acidity is different in each case, as is also the nitrogen content. The specific polysaccharides of Types II and III were obtained entirely nitrogen-free within the limit of the micro-Kjeldahl method, thus proving that these sugars actually did have the immunological properties ascribed to them, because they were reactive up to dilutions of one to ten million or so and contained no nitrogen, the element characteristic of proteins.

The Type I substance was very different from Types II and III in that respect, because it contained a high percentage of nitrogen, and part of this reacted as amino-nitrogen. The whole molecule went to pieces when it was treated with nitrous acid, a reagent for amino-nitrogen. The Type IV substance, which had much the same amount of nitrogen, differed because it did not show any amino-nitrogen. There were also large differences in the acetyl content and in the amount of sugar acids derivable from each of the polysaccharides. The acetyl group of the Type I substance is on an oxygen atom, and when it is lost, the immunologic properties of the polysaccharide are very much weakened. The acetyl group in Type IV is on a nitrogen atom and is very difficult to remove. It thus appears that there are very definite chemical differences which determine the immunologic specificity of these carbohydrates.

When one injects Type III or VIII pneumococci into animals, one gets antiserums which cross-react. The Type VIII serums give a certain amount of precipitate with Type III pneumococcus polysaccharide, and the Type III serums precipitate with Type VIII polysaccharide, and in the same way the heterologous serum agglutinates pneumococci of the opposite type. The reason for this behavior is that the same uronic acid is present in each of these two polysaccharides, although in different

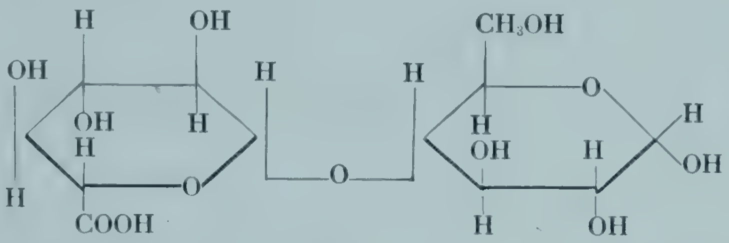
TABLE 16

PROPERTIES OF IMMUNOLOGICALLY SPECIFIC POLYSACCHARIDES OF PNEUMOCOCCUS

Type	*N Content*	*Rotation of Polarized Light*	*Neutral Equivalent*	*Acetyl Content*	*Uronic Anhydride Content*	*Reducing Sugars after Hydrolysis*	*Relative Viscosity 0.2% in H_2O*	*Relative Viscosity 0.1% in 0.9% NaCl*
	per cent			per cent	per cent	per cent		
I	4.6*	+280°	650	7.1†	56	30	9	1.7
II	0.2	+55°	950	1	18	95	11	1.6
III	0.1	—33°	340	0.5	50	85	32	3.0
IV	5.5	+30°	1500	5.8‡		71		
VIII	0.2	+123°	720	0.5	27	87	17	2.5

* About one-half reacts as NH_2 N.
† Reacts as O-acetyl.
‡ Reacts as N-acetyl.

amount. The accompanying diagram shows the structural formula for this uronic acid.[6] In both polysaccharides the glucuronic acid is linked to another molecule of glucose, and this form of linkage, which is indicated by the light and heavy lines, as in the type of formula introduced by Haworth to show the space relationships of the sugars, indicates that this is cellobiuronic acid.



If the carboxyl group of the uronic acid were CH_2OH, instead, there would be two molecules of glucose linked as cellobiose which is derived from cellulose, but in these two pneumococcus polysaccharides there is the acid or cellobiuronic unit of structure. The Type III polysaccharide is composed of X of these units, a long chain of a very large number of double sugar-sugar acid units. The Type VIII polysaccharide has the same units, but with two extra glucose molecules between. This suffices to cause a certain amount of immunologic crossing, because there is a multiple occurrence of these characteristic cellobiuronic acid units.

Just as in the case of proteins it is known or at least assumed that the multiple appearance of certain units confers antigenicity, so in these polysaccharides, the multiple occurrence of the characteristic chemical unit confers a definite type of immunologic specificity on these molecules, and when the same unit occurs multiple in different polysaccharides there is sufficient relationship for immunologic crossing.

As an interesting illustration of this, recently scientists of the Eastman Kodak Company[7] found that if they took ordinary cotton and oxidized it in the dry state, they altered some of the CH_2OH end-groups characteristic of the cellobiose units of which cellulose is made up, cellulose being the principal polysaccharide of cotton. They converted some of these into carboxyl, COOH, groups and in that way changed some of the glucose molecules in the chain into glucuronic acid molecules. Necessarily, then, this oxidized cotton contained cellobiuronic acid groupings which are the same groupings as occur in Type III and Type VIII pneumococcus polysaccharides. The prediction was therefore made that this soluble oxidized cotton would be found to be an immunologically specific polysaccharide. I secured some and added a neutralized solution of it to Type III antipneumococcus and Type VIII antipneumococcus serum, and got specific precipitates. It was the part of the antibody which showed the III-VIII cross reaction which reacted with the oxidized cotton, because that is the part of the antibody which apparently is directed toward these cellobiuronic acid units, regardless of the method by which they are linked. The actual linkage of the units in all these polysaccharides is different, but the multiple occurrence of the units determines the nature of the specificity.

Such reactions have some bearing on allergic phenomena, because it does not take very much change to convert cotton cloth into an immunologically specific polysaccharide. A little oxidation will effect this change, and possibly some of the troubles that are due to clothing may arise from actual alteration products, and not from the primary substances themselves.

In the case of the Type III pneumococcus polysaccharide there is proof that it is the multiple occurrence of the reactive unit which is responsible for the specific precipitation, because Kendall and I[8] some years ago found that we could degrade the polysaccharide to an immunologically reactive fragment containing two of these units. The single unit no longer gave precipitation, but two were enough to form a definite specific precipitate in antipneumococcus Type III horse serum, and the more units there are the more antibody reacts. So there is definite evidence that the multiplicity of the immunologically reactive or chemical grouping is the antigenic factor. Here "antigenic" is used in the loose sense of reacting with antibodies, although it is known that the polysaccharides themselves are antigenic in mice and in men, but not in rabbits.

In short, the nature of the antibody response depends on the chemical nature of the antigen. The antibodies to Type I polysaccharide react only with Type I polysaccharide and not Type II or Type III.

Antibodies

In the discussion of antibodies we are not on quite such firm ground as in the case of antigens. In the first place, it is rather uncertain where antibodies are produced in the body and what cells are responsible. In a general way it is known that if one injects into an animal an antigen in particulate form it can be followed microscopically, and is observed to be taken up by the cells of the so-called reticulo-endothelial system. Much of the antigen finds its way into the liver, much into the capillary linings, and some into the lymph glands and the bone marrow, and wherever else the reticulo-endothelial cells are present in largest number. So these cells must have something to do with antibody formation, but what is the actual process—what are antibodies?

Nature of Antibodies. It now appears certain that antibodies are actually modified serum globulins. There used to be some idea that they were non-protein substances merely carried along with the serum globulins, but since the introduction of quantitative analytical methods for measuring antibodies, the actual isolation of antibodies in large amount and the subjection of these substances to the rigid criteria to which other proteins have been subjected, there is no longer any doubt whatsoever but that antibodies are actually modified serum globulins.

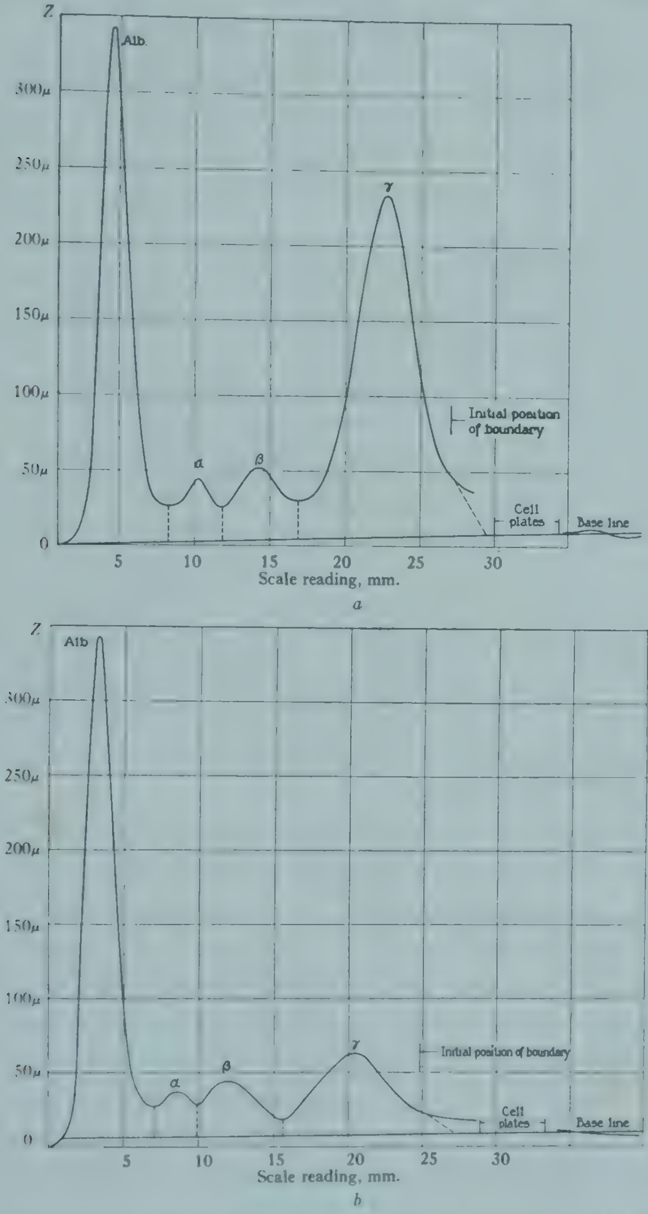


Fig. 8.—Electrophoresis scale diagram of anti-egg albumin rabbit serum 431-5 1:4 before (*a*) and after (*b*) absorption of the antibody. (Tiselius and Kabat: Journal of Experimental Medicine, *69*:119, 1939.)

The question to be answered is, how are they modified?, and about this very little is known. One bit of evidence for the protein nature of antibodies is portrayed in Figure 8, taken from Tiselius and Kabat's article on the electrophoretic properties of antibodies. The lower diagram might well be an electrophoretic diagram of normal rabbit serum, but it happens to be the electrophoretic diagram of the same rabbit serum shown in the upper diagram after the egg albumin antibody was taken out quantitatively by the addition of egg albumin. One sees, therefore, not only by the actual weight of nitrogen removed, which was determined in this case and which agreed with the difference in the areas under the gamma globulin peaks in the Tiselius apparatus, but also by the return of the electrophoretic diagram to the pattern characteristic of normal serum, that the antibody in this case is in the so-called gamma globulin fraction and forms a very large portion of that protein fraction.

In Table 17 are summarized some of the data on highly purified antibody preparations of various types from various animals. These are typical globulins, some of them about the size of normal serum globulins, others very much larger. The only large antibody that has been recorded so far in the rabbit is the hemolysin against sheep red cells. The horse, cow and pig, with certain antigens, produce large antibody molecules with a high sedimentation constant in the ultracentrifuge, low diffusion velocity and high molecular weight. Other antigens such as diphtheria toxin, in the same animal or same species of animal, produce an antibody indistinguishable in its physical constants from the principal component of ordinary globulin, like the antibodies ordinarily produced in the rabbit.

Although these antibodies are proteins, it is not known how they differ from the normal globulins, except that they are formed under the stimulus of the antigen and differ in a qualitative way which makes it possible for them to react with antigen.

Formation of Antibodies. The first theory to account for antibody formation and which seemed to give a partial reason for it was that of Buchner. He thought that fragments of the antigen actually entered into the antibody molecule and that that was why it was specific. This idea is not a very plausible one to the chemist and physicist because they know that like more often repels like than attracts it, so that this would be a reason for the antibodies not to react with the antigen. With better methods of analysis it was also found that antibodies to proteins containing arsenic, which was introduced artificially, did not contain any arsenic, even when the immune reaction was characteristic of the arsenic-containing portion of the molecule. This has been demonstrated by other means also, so that the Buchner hypothesis is no longer tenable.

The most plausible theory, but still without experimental support, is that originated by Breinl and Haurowitz.[9] This postulates that the antigen or immunologically reactive fragments of the antigen penetrate to the site of globulin synthesis, wherever that may be, and so modify the globulin synthesis—perhaps through an actual spatial disturbance by their very presence there—that the globulin which is produced is a little different from the ordinary globulin, and when it goes out into the blood

TABLE 17

Physical Constants of Purified Antibody Solutions Prepared from Animal Antiserums

Animal Immunized	*Antiserum Produced to*	*Sedimentation Constant* $S_{20} \times 10^{13}$	*Diffusion Constant* $D \times 10^7$	*Molecular Weight*	*Frictional Ratio* f/fo	*Isoelectric Point*
Horse	Pneumococcus	19.3	1.80	920,000	2.0	4.4
	Diphtheria toxin	7.2	3.90	184,000	1.4	
	Same antitoxin digested with pepsin	5.7	5.0	113,000	1.3	
	Same antitoxin digested with trypsin and crystallized	5.5	5.7	90,000	1.23	7.0
Cow	Pneumococcus	18.1	1.69	910,000	2.0	4.8
Pig	Pneumococcus	18.0	1.64	930,000	2.0	5.1
Rabbit	Pneumococcus					
	Egg albumin	7.0	4.23	157,000	1.4	5.8
	Serum albumin					
	Sheep red cells	18.9*				
Monkey	Pneumococcus	6.7	4.08	157,000	1.5	
Man	Pneumococcus	7.4	3.60	195,000	1.5	
	Syphilis (Wassermann)	36.5*		1,130,000*		

* From measurements on whole serum.
Kabat, E. A.: J. Immunol., *47*:513, 1943.

stream, if it ever happens to meet the antigen again it is so modified that it can react with the antigen.

Mudd[10] presented a variant of this hypothesis somewhat later. Pauling[11] described this very graphically, also entirely without experimental evidence, picturing the antigen with at least two identical immunologically reactive groupings penetrating to the site within the cell or on the cell surface at which globulin molecules are spun out. Because the antigen is there, the configuration of the synthesizing globulin molecule is so modified that it curls up in complementary fashion to form end-groups which are capable of reacting with the antigen when they break loose and meet the antigen again. There are some difficulties in the Pauling theory, because there is no *a priori* reason why these end-groups should ever break loose, and there is also no *a priori* reason why the antigen should remain for as long as antibodies are present, and Pauling considers this to be a necessary requirement of his hypothesis.

No one seems to have proved that antigens disappear before their corresponding antibodies disappear, but Burnet[12] has proposed an alternative hypothesis in which only the synthesizing enzyme, a kind of framework for the globulin synthesis, is modified by the presence of the antigen. This enzyme then synthesizes partial replicas of itself and keeps on passing modified globulin molecules out from the point of synthesis. Such a process would keep on after the antigen is digested or removed, and it also would explain why antibodies formed by hyperimmunization are often of a broader range of specificity, or a different type of specificity, than the very first antibodies formed.

None of these alternative theories of antibody formation is wholly satisfactory, chiefly because they lack experimental basis. Another entirely hypothetical approach, although it is based on experiments, was made by Dr. Florence Sabin[13] working with a red protein dye. She followed this microscopically into the macrophages in the omentum and the lymph glands. Having previously found that it was characteristic of normal macrophages at certain stages of their development to evolve wavy surface films, which eventually disappeared, she believes that it is the macrophages which are responsible for normal globulin formation. There is some embryologic evidence for this in the work she has done on the spleen. She finds that the particles of antigen or molecules of antigen are taken up by the macrophages and believes that they modify the globulin synthesis by their presence, and that when these surface films are thrown off from macrophages containing the antigen or its degradation products, the resulting globulin is actually antibody. Although there is some microscopic evidence for this, other experimental evidence is lacking. The theory is a combination of certain embryologic data and microscopic and anatomic observations, but beyond that it is mainly hypothesis.

Antigen-Antibody Reactions

Since antibodies are proteins it is quite possible, at least, that the antibody like the antigen is multivalent and that it has more than one immunologically reactive group on it. Most of the data available on immune reactions are interpretable on the basis that there are at least two antibody groupings on antibody molecules, that antibodies are bivalent or possibly of higher valence. This assumption provides for the first time a reasonable explanation of why a specific precipitate forms. If I add a pneumococcus polysaccharide, Type II (1:5000), which is perfectly soluble, to a little homologous antiserum, Type II antipneumococcus horse serum, then these two soluble substances, polysaccharide and antibody, immediately begin to form a precipitate which in time will settle to the bottom, and eventually there will be quite a large amount of the insoluble precipitated material. Does this happen because they have the same specificity? It is known from chemical evidence that the polysaccharide is multivalent. Protein antigens are thought to be multivalent and if it is assumed that the antibody also has at least two valences then there is an immediate explanation for this specificity.

By "valence" here is meant immunologically reactive groupings without trying to specify what they are, other than that they are made up of perhaps a large number of polypeptide groupings, perhaps several polypeptide chains held together by secondary hydrogen bonds and forming a fairly large area of the molecular surface. If there are two of them, and if there is more than one grouping on the antigen, a molecule of antigen reacting with a molecule of antibody would still have other groupings left on it to react with other molecules of antibody, and the antibody would still have another grouping or more left to react with either the same polysaccharide or other molecules of polysaccharide. In that way there would be bridge linkages between molecules and aggregates until an enormous aggregate would be built up which would either fall out of its own weight or, because so many charged groupings are brought together, would lose some of its electrical charges and some of its affinity for water. This is a simple explanation for immune reactions such as the precipitin reaction.

If the antigen is a bacterium, or on the surface of a bacterium, then agglutination occurs and for the same reason. There are thousands of antibody molecules actually holding together in direct chemical union adjacent bacteria until large clumps are formed which fall to the bottom of the tube. This theory simplifies a great many of the phenomena of immunity, but it is still to some extent a controversial matter.

Mechanism of Toxin-Antitoxin Combination. If one takes an ordinary antipneumococcus serum, or a rabbit anti-egg albumin serum, or almost any other antiserum, one finds that the very smallest amount of antigen that can possibly be added gives a very small amount of precipitate. As the amount of antigen is increased more and more precipitate is obtained, but relatively less with each successive addition, until finally a maximum is reached and with further additions of antigen the so-called inhibition zone is entered, the amount of precipitate falls off and sometimes there is no precipitate with very large excesses of antigen. This behavior is characteristic of the so-called precipitin reaction, and many antigen-antibody systems behave in this way.

But there is another very large group of antigen-antibody systems in which apparently the conditions of mutual multivalence leading to precipitation are satisfied only in the narrow equivalence region. This is called the equivalence zone of the precipitin reaction where, under ordinary circumstances, if a single antigen is used there is neither antigen nor antibody in the supernatant fluid. That is, with these relative quantities of the two components, antigen and antibody, they are completely precipitated. Pappenheimer and Robinson[14] found that the entire precipitation zone of the toxin-antitoxin reaction is really the portion considered the equivalence zone of the precipitin reaction, and that perhaps on account of the dissymmetry of the molecules involved and the disproportionate numbers of toxin and antitoxin molecules on both sides of the equivalence zone, the compounds which were actually shown to exist by ultracentrifugal methods were soluble and not insoluble. Only where the composition ranged from about TA in molecular terms, that is, one molecule of toxin to one of antitoxin, to TA_3, did precipitation occur, and at the point of most rapid flocculation, the so-called flocculation point, the composition was TA_2.

This fact can be put to a practical use, because one may take an unknown toxin and an unknown antitoxin and determine the flocculation point, the point at which the most rapid flocculation occurs, and the floccules can be analyzed and their total nitrogen can be determined. From the actual molecular composition, TA_2, knowing the molecular weight of both toxin and antitoxin, one can calculate the amount of actual toxin in an unknown toxin and the amount of antitoxin in an unknown antitoxin from the same set of analyses. These calculations should be made use of much more extensively.

The Danysz Phenomenon. Another factor in all types of precipitin reactions is illustrated by the so-called Danysz phenomenon. Let us suppose that it takes 1 mg. of antigen, when added all at once, to precipitate 10 mg. of antibody. If the milligram of antigen is added fractionally, however, it is found that before 0.875 or 0.9 mg. of antigen is added all the precipitable antibody has separated. This is due partly to the fact that in the region of antibody excess there is a different compound, corresponding to TA_3, and this is first thrown out. When the next portion of antigen is added T_2A_5 and TA_2 are thrown out. By this time all antibody has been precipitated with smaller quantities of antigen, because

TABLE 18

Residual, Incomplete or "Univalent" Antibody

Antigen-Antibody System	*Temperature of Reaction*	*Maximum Specifically Precipitable N*	*Antibody N Precipitated Serially*	*Non-Precipitating Antibody N*	*Fraction of Specifically Precipitable N*	*Portion Precipitated by Addition to sp.ppt.*
	degrees C.	mg.	mg.	mg.	per cent	per cent
Pn SIII-anti SIII, H	37	9.25	7.51	1.75	19	9*
" " "	0	10.65	8.76	1.89	18	
" " "	0	6.45	4.65	1.80	28	
Dye-Antidye, R	0	1.13	0.94	0.19	17	
" " "	0	2.0	1.59	0.41	21	
Ea-Anti Ea, R	0	14.55	11.34	3.21	22	72
H Sa-Anti Sa, R	0	6.60	6.12	0.48	7	67
Tg-Anti Tg,R	0	5.11	4.47	0.64	13	
" " "	0	1.55	0.76	0.79†	51	
Ea-Anti Ea, H (early bleeding)	0	0		0.18	100	

H indicates horse serum; R, rabbit; Ea, egg albumin; "dye," R-salt-azo-biphenyl-azo-Ea; Sa, serum albumin; Tg, thyroglobulin.

* Precipitated on chilling and letting stand.

† Residual antibody in other Tg serial experiments varied from 5 to 25 per cent of the total.

in the part of the reaction range in which antibody is in relative excess, more antibody is in the insoluble compound. It is capable of combining in multiple proportions because it has been shown that there may be up to five or six immunologically reactive groupings on most antigens. Since each of the groupings may combine with an antibody molecule there may be compounds containing a great deal more antibody than in the equivalence region.

If antigen is added fractionally, one often finds a state of affairs such as shown in Table 18. We have called the non-precipitable antibody univalent antibody, because by itself it seems incapable of forming a precipitate, but if it is added to a precipitate containing a relative excess of antigen, then it is capable of combining with it and forming an insoluble compound. For instance, with the pneumococcus Type III polysaccharide and antibodies to Type III pneumococcus, the amount of specifically precipitable nitrogen in this amount of serum was 9.25 mg., as found by adding the polysaccharide in slight excess all at once. That is the maximum obtainable under these conditions. If the carbohydrate is added in small portions there is a deficit of 1.7 mg. of antibody nitrogen precipitated, or, roughly, 20 per cent, and part of that is precipitated by addition to another III-anti-III specific precipitate. If, for instance, a specific precipitate containing 2 mg. of nitrogen is added to this non-precipitating antibody, a fraction of it, at least, precipitates, in some cases quite a large fraction. It is not known why the rest of it does not precipitate, but there may, of course, be a combination of analytical errors in the many analyses involved. If Type III pneumococci are used, which are solid and have the polysaccharide on the reactive surfaces, one may draw out the univalent antibody on these solid particles, too, by actual specific chemical combination.

Just what relation this bears to either the inhibiting antibody in post-treatment hay fever patients or to the passive transfer antibody, I am not prepared to say. I have looked for that type of antibody in the serums of patients suffering from allergies, but I have never been able to find it. That may be because the amounts are too small to determine analytically by the micro-Kjeldahl methods hitherto used.

Quantitative Determination of Antibody

There are a number of precautions that need to be taken when antibody determinations are made in human serum, which are not generally understood, and perhaps if all the necessary precautions are taken, evidence of actual specific precipitation might be found there, since it is now possible to determine a single gamma of antibody nitrogen. The error is probably 100 per cent if there is only one gamma, but if there are 5 gammas of antibody nitrogen and 5 ml. of serum a quantitative determination can be made, with an error of perhaps 20 per cent. This is now an even more sensitive test than complement fixation, because complete complement fixation fades out around 0.1 gamma of antibody nitrogen, and that amount must be in 0.02 or 0.05 ml. in order to make the test practicable. But here one can have 5 gammas in 5 ml. and still be able to determine it analytically.

Removal of Complement. The first step in the analysis is to remove the complement, and this is an important step because, contrary to general belief, complement is not an aid in immune reactions of this type; it is a hindrance. In lytic reactions, such as hemolysis, complement is necessary, and the lysis of bacteria does not take place in the absence of complement or its four components. On the other hand, precipitin reactions and agglutinations are actually slowed down by complement, and if there is only a very little antibody they may be completely inhibited.

The best way to get rid of the effect of complement is to take it out, but this may be rather difficult in the case of very small quantities of antibody, because if the serum is inactivated by heat, this may destroy or partially destroy a few hundredths of a milligram of antibody nitrogen.

Mayer and I[15] have proposed getting rid of the complement in human serum by adding an unrelated immune system which is known to fix complement. If, for example, the serum to be analyzed is from a patient recovered from Type III pneumonia as a result of sulfadiazine therapy and we want to find out how much antibody to Type III pneumococcus is in the patient's serum, we use an unrelated system, such as egg albumin and rabbit anti-egg albumin, which takes out complement in combining. We have found that 0.4 mg. of rabbit anti-egg albumin nitrogen is enough to take out all the complement activity, and all the complement nitrogen, incidentally, from 5 ml. of human serum. We therefore add 0.4 mg. of anti-egg albumin nitrogen and then 0.04 mg. of crystalline egg albumin nitrogen, under sterile precautions, and mix thoroughly. The precipitate which forms combines chemically with the complement, including most of its components, and brings it down. It is centrifuged off, and we work with the clear supernatant fluid.

Removal of C Substance Antibody. Before we can determine type-specific antibody in the serum of patients recovered from pneumonia, the antibody to C substance must be taken out, because, unfortunately, our method of chemical purification is not ideal, and almost all samples of the type-specific polysaccharides contain varying amounts of pneumococcus C substance, which is the somatic polysaccharide. In the pathogenic pneumococci there is the central nucleus and the capsular slimy type-specific substance which we have called S, and in the naked cell there is pneumococcus protein, probably several proteins, and a polysaccharide first discovered by Avery, Tillett and Francis,[16] which they called C substance, and which is common to all pneumococcus types.

This perhaps has something to do with a few cases of allergy. Practically all human beings carry pneumococci of one type or another in their noses and throats, and we have found that nearly all human serums contain more or less antibody to pneumococcus C substance.[17] The pneumococcus is a common inhabitant of the nose and throat, and this is probably the reason that this antibody is present. This C antibody should be distinguished from the C reactive protein which Avery and his collaborators[18] found in many infections, but which was present only during the febrile phase. There is a substance in the serum of patients with all sorts of fevers which apparently unites, because of certain chemical linkages about which nothing is known, with protein in the patient's serum, and which reacts with pneumococcus C substance, but this is in the albumin fraction. We have carefully fractionated the antibody to pneumococcus C substance estimated in these serums and found it to be real antibody in the globulin fraction. We can, therefore, be very definite about the fact that the serums of almost all normal human beings and of patients recovered from pneumonia contain varying amounts of antibody to pneumococcus C substance.

Therefore, because the type-specific polysaccharides usually contain small amounts of C substance, we must remove the antibody to the C substance first in order to be sure that we are getting only type-specific antibody when we add type-specific polysaccharide. Very often patients who have had their infection abruptly terminated by treatment with sulfadiazine have more anti-C than actual type-specific antibody in their serums. Very often there is no type-specific antibody at all.

The supernatant fluid is taken from the decomplementation and, with sterile pipets, set up in three portions in sterile tubes.[19] One portion serves as a blank. The other two are treated with 0.01 mg. of pneumococcus C substance, preferably either from R organisms without type-specific polysaccharides, or from another type than the one that infected the patient. These are mixed thoroughly with a sterile rod, the tubes are capped with sterile caps and put in the water bath at 37° C. for an hour or so, and then let stand eight to ten days in the icebox. If this is not done, all the antibody is not precipitated, especially when there is very little. Occasionally it may precipitate immediately, but if there are only a few gamma or a few hundredths of a milligram the tests must stand a week or ten days. Possibly if this were done with some allergic serums, one might actually find precipitating antibodies. One can ascertain that any deposit is not bacterial growth, or any non-specific substance, by means of the control tube and by smears of the precipitates.

The precipitates are eventually centrifuged off and very carefully washed with chilled saline until all non-specific nitrogen is removed. They are then dissolved in alkali and the blue color characteristic of the tyrosine molecules in proteins is brought out with the Folin reagent

This is an indirect protein nitrogen estimation and is checked against the color value from a known amount of antibody nitrogen, taking aliquot portions of larger samples of nitrogen estimated by the micro-Kjeldahl method. The two agree very closely when there is enough antibody to use both methods, and the method is accurate down to a few gammas of antibody nitrogen in a few cubic centimeters of serum, so that it is perhaps the most sensitive estimation of antibodies that has been devised to date. It is much more sensitive than complement fixation. Although this test requires more serum than does the one for the complement fixation reaction, the actual concentration of antibody which can be detected this way is much lower.

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Section II

ALLERGY OF THE BRONCHI (ASTHMA)

Asthma, or more specifically bronchial asthma in order to emphasize and differentiate it from the so-called cardiac or renal asthma, is one of the recognized diseases of allergy. Dyspnea, which is the outstanding symptom, is caused by bronchial and especially bronchiolar obstruction generally throughout both lungs. Asthma may occur as intermittent attacks or be continuous with exacerbations of varying degree. When severe and continuous the condition is spoken of as status asthmaticus.

There is a disposition today to speak of asthma as a symptom. If having characteristic signs, symptoms and pathology constitutes a disease, as most will agree, then definitely asthma is a disease. When speaking of symptoms, dyspnea is the correct term, not asthma.

If one views the subject broadly, asthma quite naturally divides itself into two types: one, the "non-infective," in which inhalants, foods, drugs and therapeutic serums are the allergens acting through or by means of an immunologic mechanism, the skin-sensitizing antibody. This antibody is bound to the cells of the bronchial mucous membrane and is also attached to the cells of the skin, making possible the skin test as an indicator of bronchial allergy. Excess antibody is usually free in the serum, hence passive transfer tests may indicate the allergen. Exceptions to this are noted with certain non-protein drugs and with that type of "delayed" allergy to foods considered in the general discussion of allergy (see p. 27).

The second type, designated as "infective" asthma, is essentially synonymous with that frequently spoken of as "intrinsic." It is the manifestation of a bacterial allergy and is based upon an essentially different immunology from that operating in non-infective asthma. In other words, the two types are distinguished on the basis of their disparate causes and allergic mechanisms.

While it is true that at least 15 to 20 per cent of the cases of asthma exemplify both types, that is, asthmatic attacks may be caused by inhalants and foods as well as infection, the subject lends itself to clearer exposition when separately discussed as "*non-infective asthma*" and "*infective asthma*."

6. *Non-infective Asthma*

W. C. SPAIN

Introduction

THE word "asthma" has been used as a synonym for breathlessness or gasping due to bodily effort from a time long before the Greeks applied it to Leander's condition just after he swam the Hellespont. In recent centuries, however, it has been restricted to medical usage, being applied to dyspnea of various pathologic states, such as the laborious breathing due to cardiorenal disease; to mechanical obstruction as from thymic enlargement, bronchial or mediastinal new growths, or polypi; or to the paroxysmal recurrent obstruction of bronchial lumina of allergic origin.

The differentiation of these several forms of breathlessness is considered in Chapter 8, but the one which is of special interest here, bronchial asthma, is unique in being chiefly an expiratory dyspnea, with relatively effortless inspiration. The recurring intermittent paroxysms have a sudden onset and offset, often dramatically abrupt, last from a few minutes to days, and in the milder uncomplicated cases, leave the patient apparently uninjured, without indications of physical damage other than exhaustion.

Such attacks of bronchial asthma are evidences of a profound tissue reaction of the patient to substances to which, through inherited capacities, he has become allergically responsive. Such antigenic substances may have been present in the patient's environment for a brief or for prolonged periods of time before a susceptibility or a sensitization has developed to them. The mechanism involved in the allergic state has been discussed in Chapter 2, but it may be pointed out that it is primarily with the prevention of antigenic contact or, if this is impossible, with the lessening of this sensitiveness which has developed to absorbed antigenic substances, that the treatment of bronchial asthma is concerned.

Antigens of Asthma. The exciting factors or antigens which may produce attacks of asthma form a heterogeneous group; many are not even protein material; but it may be said that they are ordinary substances frequently found in the average person's environment and with which he may come into active and daily contact, in the air he breathes, the food he eats, or the infections he harbors. Antigens may therefore be divided very practically, according to their avenue of approach,[1] into three groups: (1) air-borne substances, (2) foods and drugs, (3) infective agents. There are two additional groups of less importance comprising antigens absorbed by injections, and by contact with the unbroken skin.

The antigens of consequence in the first or air-borne group include pollens and molds; household and shop dusts, animal and vegetable emanations, lints of silk, cotton, flax and wool; in the second group, food and drugs; in the third, bacteria. The antigens of the first two groups differ from those operative in the third group, the bacteria, in one highly important particular—that of viability. All other antigens are inanimate particles within the body, but those of the third group remain alive, flourish and reproduce themselves. The inhalants, foods and drugs, are the products of growth and development which have occurred outside the human body before their entrance as antigens into the tissues of the individual. They have their greatest antigenic possibilities at the moment of absorption; incapable of further life within the body they are neutralized and destroyed, being replaced only after further antigenic absorption through repeated or continued contact of the individual with extra-somatic sources. On the other hand the bacterial products, the antigens of the third group, develop chiefly within the individual only after the organisms, invading in numbers initially ineffective, have had sufficient time for establishment and proliferation. The bacteria reach their greatest antigenic possibilities after growth within the body, since they are constantly produced and constantly replaced within the tissues. The reproductive activity of such sources of antigenic material explains the persistence, chronicity and increasing severity of asthmatic attacks of infective origin despite seasonal, environmental and therapeutic influences. It also accounts for many points of dissimilarity between the infective group and the inhalant and food groups due to non-viable, non-infective, exogenetic causes.

Nomenclature. Many unsuccessful attempts have been made to furnish adequate descriptive terms for these two basic forms of asthma, non-infective and infective. For instance it was once thought that the presence or absence of the inheritance feature in allergy could be used as a criterion. It was considered that non-infective asthma was an inherited form of hypersensitiveness while infective asthma was not. Coca and Cooke[2] accordingly proposed the term "atopy" to designate the inherited form of human hypersensitiveness, having in mind the non-infective group, comprising inhalant and food sensitive cases; and the term "non-atopic" was applied by them to infective asthma. Subsequently Cooke[3] showed that infective asthma also was an inherited form of sensitiveness, so that the designation "atopy" can no longer be employed as a means of differentiation. An attempt has been made to salvage the term by ascribing to it a quite different meaning, by restricting it to those cases of allergy in which it is possible to demonstrate positive immediate skin tests as characterized by the pseudopod wheal formation to the specific antigen. This application of "atopy" is unfortunate since, due to its presence in the literature with this double meaning, it is now necessary to determine whether the term is employed according to the original meaning or according to the interpretation subsequently proposed. This has led to much confusion. The term "atopy" has therefore outlived its usefulness and since it does not afford a means of differentiating basic forms of allergy it should be dropped.

The term "extrinsic" was employed originally by Salter.[4] With an entirely different meaning it was used later by Walker[5] and by Rackemann[6] to describe the non-infective groups. This is unsatisfactory, since the term suggests a superficial non-essential quality which certainly is not a characteristic of asthma due to inhalants and foods. Likewise the term "intrinsic" is not descriptive of infective asthma, since it signifies that the causative factors are inherent, essential and natural, belonging to the subject in its very existence.

The truth is that no terms are altogether satisfactory. I am tempted to offer "exogenic" as a term more descriptive of the non-infective group and "endogenic" to designate the infective group whose exciting factors develop within the body. For the present I shall designate bronchial asthma due to inhalants and foods (the types of antigens which are nonviable, and of extrasomatic development) by the rather negative and somewhat nondescript expression "non-infective bronchial asthma"; while bronchial asthma due to bacteria is discussed in Chapter 7 under the term "infective asthma."

The strong hereditary influences active in non-infective asthma have been discussed in Chapter 1 and need not be considered here. It should be emphasized again, however, that it is the capacity to become asthmatic which is inherited and not the asthmatic state itself complete with specific etiologic factors. It is the impact of the environment, physical and dietary, upon this latent capacity which probably determines the specific etiologic factors, and possibly the clinical form, such as bronchial asthma.

The majority of the cases of asthma due to food sensitization develop by the age of ten years while the majority due to inhalant substances appear by the age of thirty. Non-infective asthma may therefore be considered as an affliction largely of childhood and youth, in contrast to infective asthma cases which show their first symptoms in infancy and after the age of thirty (a general rule to which there are many exceptions).

Little is known of other important, but often obscure, influences such as the endocrine factors, of menstruation, pregnancy and menopause,[8] of the effect of fatigue, vasomotor instability, or of nervous and psychic elements.[9] It is generally agreed, however, that these are secondary factors, active in established, usually chronic cases, and that in themselves alone they cannot initiate the asthmatic state.

Incidence

Asthma is relatively common, sharing about equally with hay fever an incidence of about 3.5 per cent of the general population.[7] Since the non-infective group comprises about 85 per cent of all cases,[1] it is evident that about one person in each one hundred is rendered asthmatic by the inhalation of air-borne substance or by the ingestion of foods or drugs. It is in this 1 per cent that we are here interested.

Symptomatology

The asthmatic seizures, with the dyspnea chiefly expiratory, occur in sharp bouts with abrupt onset and offset, interrupting periods of complete freedom. The contact with the excitant is accidental, as is the case with many inhalant or food substances. In other instances the attacks may be cumulative, daily exposure to the excitant, usually a food, being apparently without disturbing effect until finally, the tolerance being overcome, a sudden overwhelming seizure occurs; or the asthma may be low-grade, continuous with exacerbations, when there is more or less constant contact with the excitant, as in persons with asthma from pollens; from bedding; or from foods ingested each day as milk, egg or wheat.

Coryza, particularly in the inhalant cases, is very often the first evidence of a beginning attack, being associated with itching of the eyes especially at the inner canthus; or *cough* may be the first symptom, and, in minor attacks, indeed the only one. It frequently becomes very pronounced, continuous even when no associated wheezing is evident; often it is non-productive, there being little expectoration in the non-infective types of asthma. The heavy mucoid or mucopurulent sputum, produced in large amounts and considered typical of bronchial asthma, is more frequently found in the infective cases.

Abdominal pain, acute or chronic, mild or severe; *abdominal distention*; *diarrhea*, or *constipation*, may be present during attacks, especially in asthma due to foods. Allergic *skin manifestations*, as rashes or urticaria, may be associated sensitization phenomena. *Pallor* about the nostrils and mouth, a drawn, pinched expression with a duskiness of the skin, lassitude and irritability, often are the first physical evidences of a beginning attack, particularly in children. *Wheezing* usually occurs early, sibilant and sonorous râles being heard throughout the chest. The accessory muscles of respiration are called into play in the prolonged expiratory phase of respiration so that the patient assumes the hunched or "gargoyle" posture so typical of bronchial asthma, and in time, the undue stresses and strains placed by increased muscular contractions upon the growing but pliable bony cage lead to the "barrel shaped" chest, or "pigeon breast" which persists in chronic cases throughout the years.

Laboratory Data

The simple, uncomplicated case of non-infective asthma shows no abnormal changes in the urine; the routine white blood cell count is normal. The differential count shows an eosinophilia, present often only during attacks or immediately thereafter, which may reach a level of 27 per cent but is usually less.[3] A similar increase in eosinophils may be present in the nasal and bronchial secretions;[10] but this is no point of diagnostic importance in differentiating non-infective and infective asthma since cases of infective asthma exhibit as many or even more eosinophils than do the inhalant or food cases.[3] This should occasion no surprise if the persistent and stubborn nature of the bacterial excitant is recalled. The sputum is scant, mucoid and colorless. The blood chemistry and sedimentation rates are normal. X-ray films of the chest show no abnormality in the non-infective cases except possibly an increase in the hilum and bronchial markings.

Etiology

Inhalants. The exciting causes important in the inhalant type of asthma are a large and varied group of proteins of vegetable and animal origin, but they share one characteristic, their ability to occur in a finely divided powdery form which enables them to float suspended in the atmosphere for periods long enough for them to be drawn, with the inspired air, into the respiratory tract where they are absorbed. The degree of buoyancy among the inhalants is quite variable, certain pollens, as nature intended, being able in dry weather to remain in the air for days, while the animal danders, dusts and lints soon settle out.

Seasonal. Bronchial asthma shares with hay fever the disturbing effect of the air-borne group of *pollens* described in Chapter 10. In the East, the pollens of importance are those of the various hardwood trees—ash, oak, elm, beech, birch, hickory and poplar—of the various grasses and of plantain and ragweed. Ragweed pollen is the most important of all as an excitant of asthma as it occurs in tremendous quantities, over a period of six to eight weeks each year. Its season extends to a time too late to permit the recovery, in many patients, of the pollen-irritated respiratory tissues before the advent of the cold, wet weather so inducive to upper respiratory infections. It is common to find that asthma caused initially only by ragweed pollen, and therefore at first occurring only during August and September, gradually is complicated by a secondary infection of the upper respiratory tract. Such an infection may in turn be the cause of a bacterial asthma which persists for longer and longer periods into the fall and winter, far beyond the end of the pollen season, eventually becoming non-seasonal.

Frequently *non-seasonal* inhalant factors such as dusts, dog or horse epithelium or possibly foods entirely inactive at other periods may aggravate and complicate a pollen asthma during the pollen season. For this reason the possible effect of non-seasonal excitants upon the pollen victim must often be investigated, particularly when the results based on pollen therapy alone are discouraging.

While non-infective asthma with definite seasonal limits is usually of pollen origin, it may be due, especially in the tropics but also in the mid-West, particularly in the Great Lakes region, to the air-borne spores of certain *molds;* best known to us because of studies made in the United States are Alternaria, Hormodendrum, Penicillium and Aspergillus.[11, 12, 13, 14, 15] These are present in the air throughout the warm months of the year, reaching a peak in early August, usually before the advent of ragweed pollen. Seasonal asthma may also be due occasionally, again chiefly in the Great Lakes region, to the epithelial *scales* from the wings and bodies of insects such as the caddis fly and May fly, which are most abundant in the summer.[16, 17]

Non-seasonal Inhalants. HOUSE DUST. Dusts which accumulate within the home are the most important and most common of all inhalant causes of asthma, a discovery made by Cooke.[18] They are composed of many diverse substances found in the household, such as wisps of feathers from bedding and upholstery; particles of dander and saliva from house pets; toilet powders; insect powders; lint of wool, silk, kapok, cotton and linen derived from bedding, clothing, drapes and floor coverings; tobacco; molds; traces of glue from book bindings, gummed labels, furniture. Indeed, the list of inhalants to be separately considered may all be viewed as constituents of house dust. All of these can at times be identified in dusts; but in addition to them, there is in house dust a factor that is actively antigenic, individual and unique. Thus far it has defied analysis, but whatever its source or nature it is responsible for many cases of inhalant asthma.

There is also present in house dust a factor which produces a wheal which is non-specific, hence without significance. This has often led to unpardonable errors in diagnosis and treatment. To be considered positive the wheal obtained upon test to dust extract (as indeed to all other extracts) should be distinctly elevated, quite active and itching, with irregular but sharply defined pseudopodia and a surrounding zone of erythema. In almost any non-allergic skin there can be demonstrated upon test with dust extract the non-specific sluggish and inactive wheal, smoothly round in outline. This has no diagnostic value.

INDUSTRIAL DUSTS are of some importance in selected cases, particularly the dusts from shops of bakers, millers and brewers; seldom are dusts from the shops of furriers, jewelers and other craftsmen etiologically significant. Outdoor dusts consisting of soot and soil are unimportant except for a possible pollen or mold content, or occasionally for some exceptional constituent such as castor bean dust.[19, 20]

ANIMAL EMANATIONS of such household pets as the dog, cat and occasionally the rabbit become actively antigenic particularly in children, when occurring in the concentrations and at such close range as are possible within doors. Animals which are kept out of the house are rarely serious offenders, except for the cow or horse, which due to their size can produce relatively enormous quantities of dander. The saliva of animals which is actively antigenic[21] is present upon the fur or hair of the pet after it licks itself, or upon toys or furniture, and may quickly become, in dried form, an air-borne inhalant quite similar to, if not identical with, the corresponding epithelial antigen from the same source.

It should be stressed that it is not animal hair composed chiefly of keratin, an insoluble substance, which is the allergic excitant, but animal epithelium. However, the commercial use of the hair of some types of animals accounts for the importance of their epithelia, or danders, as excitants.

Cow epithelium is of some importance, being a component of many house dusts since cattle hair is used in the manufacture of a coarse felting often placed under rugs and carpeting.

Rabbit epithelium is of widespread importance since rabbit hair is used as trimming upon garments; as fur lining for gloves; and in children's fur-covered or hair-stuffed toys.

Goat hair is sometimes important since it is used in rugs, mattresses, pillows and cushions.

Silk is another salivary secretion to be mentioned here as an excitant, but its importance has become less with its successful replacement by silk substitutes such as rayon and celanese.

Glue, a fish collagen, is a very active inhalant especially in cases sensitive to fish by ingestion. In dried form it becomes an ingredient of many dusts. It is used in the making of furniture, paper boxes, books, some types of labels and stickers. Fish-sensitive allergics should be warned against moistening labels, stamps, envelopes and Christmas seals with lip or tongue; most labels are gummed with vegetable dextrin, but sooner or later, if the habit is established, fish glue will be encountered, often with untoward effects.

VEGETABLE DUSTS. Powdered orris root was once of great importance, since it was used almost universally in face powders. Now, however, the manufacturers have learned to make their products without orris; only a few products contain it. However, orris is still of consequence since it is contained in many talcum and sachet powders.

Cotton and kapok (silk floss) fibers, so extensively used in mattresses, cushions and pillows, are important antigens.

Flaxseed, acacia, tragacanth, karaya gum, used in toilet preparations for the scalp and in hand lotions and water soluble jellies, may, in dried form, become inhalants of high potency.

The inhalation of particles of tobacco and its smoke produces asthma in relatively few instances. This is particularly surprising if one recalls its almost universal use, its frequent and intimate contact with the smoker's respiratory mucosa, and its constant presence in house dusts. Tobacco holds an insignificant place as an allergic excitant in bronchial asthma. Despite the conclusions reached by some investigators in their reflections upon tobacco allergy, I am of the opinion that they have yet to prove that tobacco is an important cause of bronchial asthma. Wheal responses to tests with tobacco extracts are frequently irritative, nonspecific, and are misleading as indicators of the allergic state.

Pyrethrum powder, the pulverized blossoms of a plant of the chrysanthemum family, is used as an insecticide either alone or incorporated with other ingredients. It also is employed in a liquid or spray form. It is highly disturbing to some asthmatics.

ODORS. In extremely susceptible persons the odors of certain foods not ordinarily considered as giving off emanations may produce asthma, such as fresh eggs still in the unbroken shell; fresh meats such as beef or pork; nuts, as unbroken or unshelled Brazil nuts, pecans or English walnuts. Foods with definite odors frequently are causes of asthma by inhalation, as in the case of fish; shellfish; celery; parsley; carrots; orange; melon; grape; apple; pear.

Occasionally asthma may be caused by the inhalation of the odors of cooking such as the frying of pork and lamb fat, the boiling of carrots, string beans, beets or potatoes. These are not primary excitants, however, being effective only in those individuals having other basic causes of asthma. Other secondary inhalation factors are the odors of perfumes; toluene; benzine; gasoline; linseed oil; naphthalene flakes; delousing powders; illuminating gas; sulfur dioxide and other refrigerants used in mechanical ice boxes.

FOODS, especially the dry, dust-producing types, may at times act as excitants through inhalation. Wheat flour, cornmeal, potato flour and grain dusts may produce an occupational asthma of great severity, especially in bakers, brewers and millers. The dusts of coffee, tea, cocoa bean, vanilla bean, peanuts, spices (as mustard, cinnamon, cloves) act as excitants. Drugs such as aloes, ipecac, castor bean, lycopodium, podophyllin, which may occur in dusty form, cause asthma in those in close contact with them, as in pharmacists and drug manufacturers.

Inhalant Testing Extracts. The variety of substances responsible for the majority of cases of asthma by inhalation is actually quite limited. The following group of extracts, considered a comprehensive list, has been used for years in many allergy clinics and in private practices and has been approved by the Committee on Standards of the American Academy of Allergy. The potency of each extract is based on the requirements of the intracutaneous test, since it is presumed that this method of testing is employed. These requirements demand that extracts used for testing by the intracutaneous method be made available in concentrations just strong enough to produce positive cutaneous wheals in the specifically sensitized person. Fortunately there is usually a wide margin of safety between the concentrations satisfactory for such testing purposes, and those which are so potent as to produce overwhelming or constitutional reactions. By experience it has been learned that the potencies adopted are quite safe except for the occasional, exquisitely sensitive person who can usually be identified before testing by points in his clinical history. The potency of the extracts is expressed in protein nitrogen units per milliliter, which represents the amount of phosphotungstic acid precipitable protein nitrogen.

*Inhalant Series**

Timothy 100
Plantain 100
Ragweed 100
†House Dust 1:10
Rabbit Ep. 100
Feathers 100

Orris 100
Cottonseed 100
Tobacco 100
Dog Ep. 100
Horse Ep. 100
Goat Ep. 1000

Flaxseed 100
Silk 100
Cat Ep. 100
Horse Ser. 1:100
Insecticides 100
Kapok 100
Alternaria 100

Tests by the intracutaneous method with accurately standardized extracts (Chapter 32) are made at one visit, a row at a time, with a ten-minute interval between rows, so that in a very sensitive person testing may be discontinued before completion should a pronounced reaction occur to any test. All tests which develop a positive marked reaction should be verified by repeating the test in the same strength at the next examination; those that are not positive or only moderately so should be retested in a stronger concentration of 1000 units, except for the dust which is repeated in concentrated strength; the goat epithelium which is repeated in 5000 units; the horse serum which is repeated in 1:10 dilution.

An orderly mind might question the somewhat scrambled order of the tests, which has been so arranged purposely to prevent unpleasant reactions general or local which might occur in the individual showing excessive and multiple sensitization to related inhalants. A patient markedly sensitive to animal danders would thus be identified after the first row of inhalants had been tested by the pronounced reaction to rabbit epithelium. The other animal epithelium tests, dog, horse, goat and cat, would be omitted until subsequent tests with more dilute solutions could be attempted, thus preventing the possibility of a general reaction either from the summation of too many animal tests or from too high a degree of sensitiveness to one of them.

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* In this list Ep. means epithelium (dander), Ser. means serum.

† An extract prepared individually of the dust obtained from the home or shop of the patient may afford additional aid.

Horse serum is included in the inhalant list since it is the duty of the investigator to discover in his allergic patient any serum sensitization. Often an allergic person is dangerously sensitive to horse serum, a point of vital information to be searched out and remembered both by the investigator and the patient, as is discussed in Chapter 29.

Ingestants. *Asthma Due to Foods.* While food is undeniably a cause of bronchial asthma, it has been assigned too much importance by the lay person as well as by many physicians. The general interest in diets as such; the tendency to attribute to the ingestion of foods all manner of complaints; the deep impression made by the occasional instance in the asthmatic of the sudden, sharp, often dangerously severe attack following immediately upon the eating of a specific food, combine to give undue consequence to food allergy as a cause of asthma. An additional factor contributing to the overemphasis placed upon food allergy is the wheezing occurring so frequently in the asthmatic after overeating or even after moderate eating when fatigued, a result wrongly attributed to an allergy to food rather than correctly to a non-specific disturbance of the digestive process with resultant embarrassment to breathing.

While asthma from the ingestion of food may occur at any age, it is a state that is found chiefly in the first decade. By the age of thirty, most early food sensitizations have disappeared clinically, although not always cutaneously. The positive reaction by skin test with a food may persist long after the patient has developed a complete tolerance to it in all other respects. Throughout the centuries human beings have been more highly conditioned to intimate contact with foreign protein absorbed by way of the gastro-intestinal tract than to that absorbed through the respiratory membrane. Such contact of the gastro-intestinal membrane with food proteins may be considered normal, while the contact of the respiratory membrane with air-borne particles still remains wholly abnormal, a situation which may in part explain why food allergies tend to appear and then to disappear in the early years, often during the development of severe inhalant allergies which persist. This situation may also account for the lesser incidence of severe food allergy as well as for the fact that if present, food allergy is usually associated with an inhalant (and predominant) allergy.

While any organic material considered edible may be a specific food excitant, there are a number of substances which assume major importance either because of their high incidence as causative factors, or because of their capacity even in minute amounts to produce dangerously severe attacks of asthma. The foods with high incidence as excitants are those which man meets early in his dietary career. Listed in the order of their importance they are: egg, fish, shellfish, cow's milk, wheat, chocolate, tomato, orange; also oat, beef, and chicken. Among the foods notable for producing the most severe and most critical attacks of asthma are egg, fish, shellfish, nuts, seeds, especially mustard seed and cottonseed, and buckwheat. Extreme care must be used in testing with the extracts of these substances.

Individual members of the several groups of foods as cereals, meat, fish, fruits, vegetables, beverages, spices, have been suspected and indicated as provocateurs of asthma. No food however unusual or rarely eaten must be overlooked. In this day of processed and commercially altered foods, it is highly difficult to identify many of the basic ingredients, since the Food and Drug Administration does not require labeling sufficiently specific to be of fullest aid to the food allergic; for instance, the term "vegetable oil" means little to the asthmatic highly allergic to cottonseed oil, but quite able to tolerate soy, peanut or corn oil. The avoidance of cottonseed oil became increasingly difficult in a wartime economy, since the lack of edible fats accelerated its use in butter substitutes, in salad oil, in shortenings for baking and frying.

Food Test Extracts. A list of food tests representing the minimum requirements for an allergy clinic and approved by the Committee on Standards of the American Academy of Allergy follows, the potencies being expressed in protein nitrogen units per milliliter. When the clinical history indicates an unusual degree of clinical sensitiveness to any food, tests with extracts much weaker, from one tenth to one hundredth of those indicated, should first be used. For instance it might be extremely hazardous to employ the routine strength of egg as given, 100 units, in a patient with a history of violent nausea, vomiting and asthma from the odor of an unbroken egg, or sudden urticaria from the mere handling of it.

Series I

Milk	1000	Chicken	3500	Tea	3500
Egg	100	Pork	3500	Coffee	3500
Wheat	3500	Lamb	3500	Chocolate	3500
Rice	3500	Beef	3500	Mustard	50
Rye	3500	Codfish	100	Cocoanut	100
Oats	3500	Halibut	100	Peanut	100

Series II

Orange	3500	Strawberry	3500	Corn	3500
Grapefruit	3500	Onion	3500	Spinach	3500
Banana	3500	White Potato	3500	Cucumber	3500
Peach	3500	Celery	3500	Lima Bean	3500
Prune	3500	Cabbage	3500	Pea	3500
Apple	3500	Carrot	3500	Tomato	3500

This list is by no means comprehensive. When there is a clinical history strongly suggestive of food allergy, or positive reactions upon test to any of those enumerated, further testing may be necessary with an additional series of fruits, vegetables and nuts, as follows:

Series III

Lemon	3500	Pear	3500	Parsley	3500
Apricot	3500	Pineapple	3500	Soybean	100
Cantaloupe	3500	Honeydew Melon	3500	Sweet Potato	3500
Date	3500	Lettuce	3500	Turnip	3500
Fig	3500	Cauliflower	3500	Pecan	100
Grape	3500	Green Pea	3500	English Walnut	100

Asthma Due to Drugs. Drugs, by ingestion, produce severe attacks of asthma in a group which fortunately is relatively small. Only from evidence supplied by the patient's history, or by the physician's own observations, can the presence of such drug sensitization be established, since (see Chapter 29) the cutaneous test is usually both negative and hazardous in these cases. *Acetylsalicylic acid*, preeminent in this group, can of course be employed safely in the majority of allergic persons, but a 5-grain tablet has proven to be a lethal dose to too many asthmatics who have unsuccessfully attempted to convince the skeptical physician or nurse that aspirin was for them a deadly drug. Aspirin should never be casually or routinely prescribed for the allergic, nor should its derivatives or related products such as the salicylates, phenacetin or acetanilid, either as such, or obscured under fanciful trade names. Acetylsalicylic acid, for instance, may be camouflaged in nostrums which are offered as routine remedies for menstrual pain, headache, "colds," and in the case of one proprietary preparation, for asthma itself!

The *barbiturates* may produce asthmatic symptoms which are usually less acute, less obvious and less sudden than those produced by aspirin, especially when combined with ephedrine, which may mask or delay the symptoms. Occasionally asthma may be produced by the ingestion of the sulfa drugs, quinine, podophyllin, cascara; by the use of penicillin; or by the ingestion of glandular and vitamin preparations.

Injected Substances. Asthmatic attacks may occur from the injection of foreign protein, usually in the form of therapeutic horse serum preparations. The reaction which occurs in the person spontaneously allergic to horse serum is often profound, with intense asthma which may lead to cyanosis, shock and death from asphyxia.

Asthmatic attacks have also occurred from the administration, especially upon reinjection, of tetanus toxoid or more particularly of the broth (containing peptone) in which it has been prepared.[22] Catarrhal vaccines, autogenous or stock, have caused attacks in the infective asthmatic (Chapter 7). Asthmatic symptoms from the injection of insulin and liver extract[23, 24] have been reported many times. Penicillin, by injection, has at times produced asthma. Peanut or nut-sensitive persons have developed asthma from the injection of peanut oil[25] used as the vehicle for therapeutic substances, epinephrine or the estrogens. The occasional case of asthma following bee or wasp sting must be classed under the injectant type.[26, 27, 28]

Contactants. There is a relatively small but important group in which asthmatic attacks develop from absorption of the specific excitant through the unbroken, intact epidermis. Inhalation of the excitant often plays a part in this group and is difficult to rule out. In many instances there is an associated rash or urticaria. Egg, beef, nuts, seeds, many fruits and vegetables have produced asthma apparently by contact only. Chefs, kitchen workers and food handlers are chiefly affected. Silk has been considered to cause asthma by contact only. Among the drugs, the essential oils such as bergamot, delphinium, citronella, wintergreen, may produce asthma by contact only, as may mustard and flaxseed in poultices.

Multiple Sensitization

Seldom is the non-infective type of asthmatic patient disturbed by a single agent, unless it be a pollen; usually in each case there are many antigenic factors operative, which may be closely related, or may be quite dissimilar. The person sensitive to horse dander is usually sensitive to other animal danders too, as those of the cat, dog, cow and rabbit and, as he finds to his amazement at the circus or zoo, to those of seldom seen beasts in the cage or menagerie. The patient sensitive to cottonseed is usually sensitive to flaxseed, kapok seed, mustard seed, and often the nut group, while the person with a fish sensitization often is disturbed by seafood generally. The presence of a common factor present in related antigens may tend to explain multiple sensitizations such as those just mentioned, but it does not apply to the very considerable number of patients who are involved with a group of diverse, entirely unrelated substances. It is not uncommon to discover inhalant, food and drug factors as excitants in a single individual; a patient may become acutely asthmatic from the inhalation of dander from the horse he rides, from the ingestion of lobster in the salad he eats, from the absorption of mustard from the plaster upon his aching back.

Curiously enough, in many instances, in spite of a decidedly active positive response by cutaneous test, the irritating effect of an antigen may be so feeble clinically as not to be apparent except in the presence of an antigen more potent clinically. A young woman who, by history and by cutaneous test, is strongly sensitive to ragweed pollen develops asthma only during the late hay fever season. Severe immediate dyspnea will be produced not only by exposure to ragweed pollen, but also by the ingestion of chocolate, fish and shellfish, although these foods may be eaten with complete impunity at any other season of the year. The intracutaneous test to chocolate and seafood is as markedly positive in this patient as that to ragweed. From such an instance it would seem that many excitants which are positive by history and by test are of importance clinically only because they enjoy the support and the reinforcement of effect provided by more active factors. That this idea may be true is strengthened by the general observation that the non-infective asthmatic, sensitive to many inhalants, will show a gratifying rate of improvement when the treatment, by luck or by good judgment, has been based upon the recognition of the excitants of primary importance. Experimental justification of this idea has been furnished by Sherman,[29] who showed that in a serum obtained from a patient with multiple sensitization to such excitants as dog and horse epithelia, the addition of the antigen clinically important and active, say horse epithelium, would produce neutralization not only of the skin-sensitizing antibodies specific for horse epithelium, but of the antibodies for dog epithelium as well. Upon the addition to the serum, however, of an antigen clinically unimportant (as here, dog epithelium), the neutralization would be strictly limited to its corresponding antibody, and there would be no spread of influence to the related antibody, horse epithelium. This phenomenon is discussed more fully in Chapter 3.

Rarely is asthma the sole allergic manifestation presented by a patient. Other clinical forms are often present, such as coryza, dermatitis, urticaria and gastro-enteritis, any one or all of these forms first occurring simultaneously with the onset of the asthma, or earlier or later. The symptoms occur at the time of the asthmatic attacks, or entirely independent of them. As would be anticipated from the continuity and similarity of the respiratory tissues of the bronchi and of the nose and paranasal sinuses, allergic coryza appears most frequently as the associated condition. Indeed, it is usual to find the individual attack of asthma heralded by an acute attack of coryza which may be present for either a few seconds or for hours before the dyspnea develops, and may then persist throughout the attack of asthma. The coryza may have its onset as a clinical entity many years before the appearance of the asthmatic condition.

Diagnosis

History. The successful management of the case of bronchial asthma will depend largely upon the information obtained by analyzing the factual evidence procured by questioning the patient. The most important single aid in the proper classification of asthma, in determining basic etiologic features and in verifying the diagnosis, is the meticulously taken, comprehensive history.

Clinical Data. Of prime assistance is the assembling of the clinical data pertaining to recent attacks. It is necessary to learn of the *frequency* of the seizures, their duration in hours, days or weeks. The *severity* of the seizures is of significance in evaluating the condition, and is evidenced by the gravity of the symptoms; by the medications needed, their type, their effects, frequency of use and quantity; and by the degree of prostration following in the wake of the attack. The effect of *seasonal variation* is suggestive, the mild infective types being worse in the winter season, the severe being asthmatic all through the year. The segments of the year, May through June, and August through September, stand out prominently in the consideration of seasonal attacks, since aggravation of symptoms during these months tends to implicate pollens or molds as factors.

The effect of the *physical environment* should be noted. The disappearance of symptoms while the patient is absent from home, on vacation, or in the hospital, suggests an excitant active in the home environment although the lack of tension and rest while away may also lessen the severity of symptoms. The hospitalization of asthmatic patients in order to observe the possible changes in symptoms is a diagnostic procedure often used with benefit.

The pattern produced by the interplay of attacks and remissions should be closely analyzed. Are the attacks entirely paroxysmal separated by symptom-free stretches, or are the attacks simply exacerbations of a continually present state of dyspnea? If the former, some extraneous, extrasomatic cause is suggested, if the latter, some form of persistent upper respiratory infection.

Environmental Influences. Following the assembling of clinical data pertaining to recent attacks, there should be made an inventory of possible environmental influences. The physical factors in the home include the household pets, especially the dog and cat; the domestic animals, such as horses and cows, occasionally others; the types of furnishings, especially in the bedroom, particularly the pillows, mattresses and cushions of cotton, kapok or feathers; the presence of cattle hair felt in under-rug cushions; the use of insecticides, an extremely delicate question, always to be asked with diplomacy and tact. There should not be overlooked the occupational contacts with exciting substances as in furriers, bakers, barbers and dairymen. In the allergy clinic it should be the obligation of the social service investigator to collect this information from the patient, to corroborate it by a visit to the home and to make sure that the suggested changes are made. Questionnaires with the correlation of such data are a diagnostic essential, due to the conviction that regardless of the form of treatment, the results will be unsatisfactory if indicated environmental changes are ignored.

Dietary Factors. The dietary factors should be studied, with an analysis of the patient's food habits and food selections. Almost every asthmatic person has his individual opinion regarding what his diet must be and should be, to lessen his asthma. Idiosyncrasies, excesses and omissions from the diet should be noted, and above all, the foods considered by the patient to be highly disturbing in producing allergic symptoms. A fine knowledge of this situation may divert the physician and the patient from real disaster at subsequent skin testing. Data upon the quantities used of tobacco, coffee, tea, chocolate and alcohol are often helpful.

Of especial importance in the patient in whom the cutaneous tests with foods are negative is the close questioning of the patient regarding any food or foods he may eat immoderately, as in the case of the milk-sensitive asthmatic, negative by skin test but diagnosed simply by learning that he consumes two quarts of milk a day. It should also be learned what foods are eaten though disliked; what foods a child must be coaxed or forced to consume, his natural aversion, mistaken for a whim, being overridden by the insistence of the parent. This is often the case in the milk- or egg-sensitive child. There should be determined also the presence of any associated, perhaps minor, allergic condition which may share a common cause with the asthma, but in a more apparent way, thus making possible a diagnosis. For instance, a patient may develop both asthma and coryza from a substance such as chocolate, the former complaint obscurely, the latter quite obviously.

Drugs. Ingested drugs should be investigated, especially the coal tar group. Acetylsalicylic acid (aspirin),[30] as stated, is noted for producing acute severe attacks of asthma, and fatalities from the ingestion of as little as a 5-grain tablet have been seen. Here again carefully obtained foreknowledge will furnish the proper warning, since, luckily, acetylsalicylic acid sensitization usually increases at a moderate and recognizable pace. The patient is often fully aware of his gradually developing sensitization, is more than eager to convince you of the fact if you will only permit him to do so. Phenacetin, acetanilid, saccharine, the salicylates, the multitudinous "anti-pain" "anti-cold" nostrums, containing the coal tar drugs must be suspected. The barbiturates also are important but cause less sudden, less explosive symptoms.

The patient should be questioned concerning any previous administration of therapeutic serums or toxin-antitoxin, and as to any unpleasant experiences therefrom. Subsequently upon test with dilutions of horse serum, a procedure which should be considered routine in every allergic case studied, a positive response may signify little, being the result of the previous serum therapy; or it may be of utmost consequence, indicating a dangerous degree of spontaneous serum sensitization, knowledge important to both patient and physician.

Previous Illness. There should also be a survey of past infirmities, operations and illnesses. Chronic or acute pharyngitis, tonsillitis, repeated nose and throat treatments or operations suggest an infective asthma. The women of the home are usually the repository of such information, and should accompany to the office not only the child but the male adult, since he often tends to minimize or forget such data. There should also be a record of any earlier allergic condition since it may share the cause with the present form.

Also of importance is the recording of clinical allergies in the antecedent and collateral members of the family. The familial occurrence, unilaterally and especially bilaterally, of such conditions as asthma, pollinosis, urticaria and migraine suggests strongly that the asthmatic patient under study is highly sensitive and his asthma is more likely to be of a non-infective type.

A well taken history is a time consuming project particularly if it includes, as it should, a sifting of the patient's ideas and theories as to the causation of his symptoms. Many fantastic and worthless bits of information may be obtained, but there may be important clues among them. A history can never be completed at one sitting since questions, suggestions, ideas, occur to both physician and patient over several visits.

The act of skin testing is second in importance to obtaining the history. The history actually encompasses the testing procedure, since no tests should be made until the history is completed and consulted; and after the testing is accomplished no conclusions can be reached until the history is again consulted, this time for confirmation of the findings by test, because no test is significant without a history of clinical verification. It is quite evident that the history is of prime importance in the asthmatic who demonstrates positive skin reactions upon test; but it becomes much more important in the asthmatic who shows only negative results by test.

Technical Procedures. To anyone involved in the specific technical procedure of skin testing, it soon becomes obvious that cases of bronchial asthma divide themselves into those that give positive reactions upon test and those that do not. Furthermore, in the positively reacting group occur practically all those cases whose symptoms are due to the inhalants, and many, perhaps half, of all the cases due to foods. In the negatively reacting group are found the remaining cases sensitive to foods, the drug-sensitive cases, and the cases of infective asthma.

The inhalant and food cases comprising the group found to be skin-sensitive upon test share another characteristic, a swift reaction time, only a brief period, varying from a fraction of a second to several hours, elapsing between contact with the exciting substance and the development of symptoms. The attacks are severe, abrupt; the more extreme the degree of sensitiveness, the more sudden the appearance of asthma. The touch of egg white to the lip of the egg-sensitive infant, or the licking of a label by a glue-sensitive person may be followed, in less time than it takes to tell of it, by dyspnea, cyanosis, generalized edema, collapse and even death. A milder example is the quick asthmatic response occurring in the animal-sensitive person from contact with the horse, cat or dog.

In contrast to these are the cases of food sensitization negative by skin test, in which allergic symptoms do not develop until an interval usually of twenty-four hours or longer has elapsed following ingestion of the offending food. The failure of these patients to respond promptly either upon clinical test or upon skin test is probably due to the same cause, that is, the lack, not of the specific antibody in the tissues but of the immediately available antigen in the offending protein both of the food ingested and of the diagnostic extract skin tested. The specific antigen is presumably not the unaltered protein itself but some product of digestion or disintegration that develops during the reaction time. That this is true at least in some instances was shown by Cooke,[31] who demonstrated in a person clinically proven to be allergic to milk, with a delayed reaction time and a negative skin test for whole milk, that a definitely positive, specific skin reaction could be obtained provided the tests were made with milk proteose.

In the patient with a delayed type of reaction, who does not have the sudden and often startling onset of asthma characteristic of patients with an immediate reaction time, the attacks may be individual and isolated due to the chance ingestion of the specific food excitant; or the attacks may be periodic due to the daily ingestion of the exciting food, which occurs without incident until the irritation accumulates to the point of explosion; or the attacks may be constant due to continued contact with the food excitant. These attacks may be mild or severe, according to the degree of sensitization.

It should be reemphasized that the procedure of skin testing should not be attempted upon any patient until a comprehensive history has been obtained, since as has been said, a condition of severe sensitization may be discovered, which will influence the number and strength of the initial tests. Usually following the history-taking, tests by the intracutaneous method are completed with the series of inhalants and foods as described. Should this probe fail, all skin tests being negative, there are two diagnostic steps that may aid in identifying the cause or causes, which in the group of non-infective asthma cases are almost always among the foods. The first step is the searching analysis of the dietary habits, such as the likes and dislikes of the patient as described previously; the second step is the clinical test of suspected foods. Certain articles in the menu which demand especial attention in such an analysis have hitherto been mentioned as the most important either because of their high incidence as excitants or their extreme potency. They are milk, egg, wheat, chocolate, nuts, seeds and seafood.

If an investigation of the diet is unsuccessful, trial and error procedures may be attempted especially in the case suspected of a chronic food sensitization. A clinical test may be applied positively by adding a suspected food to the fare and checking the results for the occurrence of asthma; or it may be applied negatively by removing from the diet all foods except a sharply limited number according to the ideas of Rowe[32, 33] and Vaughan,[34] leaving one meat, two cereals, three to four fruits and four vegetables to be used in the preparation of all meals. If the patient does not become symptom-free on this regime the initial elimination diet may be replaced by a second, or a third equally restrictive and entirely different. If he becomes symptom-free, the patient is permitted to add foods singly and gradually to his menu and his behavior is observed carefully for evidence of a disturbing food.

It is often of advantage to have the patient prepare a food diary, listing carefully all foods ingested at each meal, with a final entry each day as to the presence and severity of symptoms. The relationship between the appearance of asthma and the hour of day, or the day of the week, when the suspected food was ingested may furnish a clue.

General technical methods utilized in the study of non-infective asthma are employed for differential diagnosis or for the identification of complicating conditions. They are procedures used in any general medical problem and include routine urine analysis, routine blood count, determination of the sedimentation rate, hemoglobin and blood chemistry. Often valuable is the information obtained from the Wassermann test, the basal metabolism studies and the electrocardiogram. The search for a complicating upper respiratory infection is important. The thorough physical examination, with roentgenograms of the chest, teeth and sinuses, is necessary.

Treatment

Bronchial asthma may be considered to be the clinical expression of the profound reaction which occurs in the allergic person when the tissues of the respiratory tract are subjected to the exciting agents, such as inhalants, foods, drugs or bacteria, to which they are specifically sensitized. Such attacks mark the climax of a succession of events, the most important stages of which are (1) the acquisition in the potential asthmatic through inherited tendencies of the capacity to become allergic; (2) the development in such an individual, after the inevitable exposure to specific excitants, of specific antibodies which locate chiefly but not exclusively in the tissues of the bronchial wall, especially of the mucosa, submucosa and possibly the muscularis; (3) the invasion of these tissue areas by the specific antigen, locally absorbed by inhalation, or carried thence by the lymphatics or the circulation from other areas penetrated by the antigen through inhalation or ingestion; (4) the interaction in these tissue areas of antibody and antigen, with consequent tissue irritation, as expressed by capillary permeability, edema, and/or glandular hypersecretion, leading to partial bronchial obstruction, with the consequent expiratory dyspnea known as asthma.

Specific Treatment. The specific treatment of asthma consists in efforts to interrupt this sequence of events at any of its stages. It is difficult to influence the first stage, the development of the capacity for sensitization. Certainly, in the present state of eugenics, little can be accomplished in preventing the transmission by inheritance of the disposition to become sensitized until we can discourage the intermarriage of allergic persons. A familial trait, this tendency to sensitization is stronger when the antecedent paternal and maternal allergic histories are outstanding.[7] Nor can much be done in the second stage to prevent the capacity, once it is inherited, from becoming fully developed. Persons with an allergic heritage, especially those in whom a mild allergic condition, such as coryza, has become established, should be cautioned against continued intimate contact with the common excitants such as bedding materials composed of cotton, kapok and feathers, and with domestic animals, especially household pets. Such persons, usually children, should have infected tonsils and adenoids removed to prevent the possible development of a bacterial sensitization.

Once the specific sensitization has developed in the third stage, it is possible often to prevent overwhelming contact with the antigen, especially in the group of asthmatic persons with an immediate reaction time, since in this stage speculation as to possible excitants is replaced with the knowledge of actual causes as determined by skin tests. In those persons whose asthma is found to be due entirely to removable or avoidable causes, such as a pet in the home or a food in the diet, active immunization treatment may not be necessary. Elimination of the dog from the home or egg from the diet may be sufficient and may prove to be, fortunately, the only treatment necessary.

In this attempt at eliminating or discarding all environmental excitants found important by history and by test, the bedroom demands special attention. The types of pillows, mattresses and cushions must be investigated. Feathers, cotton, kapok and wool, if indicated by test, must be removed. Large rugs, drapes and bookcases may be dust catchers. Under-rug cushions may furnish the irritation to the patient sensitive to cattle hair. Children's toys, hairy or stuffed, must be discarded in rabbit-sensitive cases. Toilet powders often must be replaced with orris-free preparations. It is not usually necessary to strip the whole house, nor need the bedroom be entirely bare and unattractive. Washable curtains and rugs may be used.

Secondary environmental factors must be considered, such as minute gas leaks in heating and lighting equipment; fumes from oil burning furnaces and from electric refrigerators; odors from cedar closets, naphthalene flakes, floor waxes.

Unfortunately in most instances the causes are not entirely removable; contact continues, symptoms persist and attempts at immunization must be devised. In other words, since the fourth stage described, the union of antigen and antibody, cannot be prevented, an effort must be made to soften the effect of the interaction with its consequent tissue irritation. In the case of the inhalants, but not of the foods, this may be accomplished by the parenteral injection of aqueous extracts of the specific excitants whose preparation is described in Chapter 32. In the course of such injection treatment there develops an immunologic product specific for each excitant, which apparently interferes with the rapid interaction of antigen and antibody, thus preventing abrupt and severe asthmatic symptoms when the person is exposed to the excitant. This immunologic product has been called a "blocking antibody" by its discoverers, Cooke, Barnard, Hebald and Stull.[35]

Once the intracutaneous testing of the inhalants has been completed and the positive reactions verified by retest, it is necessary to determine from the clinical history which of the positively reacting inhalants seem significant as excitants in the problem at hand. Obviously, positive reactions to horse epithelium would be of little clinical significance in a lighthouse keeper isolated on a horseless island, or dog epithelium reactions in a nun sequestered in a convent. Once the inhalants positive by test have been carefully evaluated and those of clinical importance selected, treatment by hypodermic injection of their extracts may be begun.

Treatment by Specific Injections. INHALANTS. In the chapter upon the preparation of extracts as well as earlier in this discussion a considerable list of excitants, both inhalants and foods, is given. It should be emphasized that this wide variety of extracts is employed for the intracutaneous test, and that only a comparatively few of them should be regarded as injection material. Sensitization to many inhalants and to practically all the foods can best be handled not by attempts at specific immunization but through the principle of avoidance and escape. Among the inhalant extracts, those of flaxseed and glue are not ordinarily used for injection purposes due to their extreme potency with risk of fatal constitutional effect. For the same reason, cottonseed and kapok seed extracts are seldom used. The injections of tobacco and insecticide (pyrethrum) extracts are unnecessary. When attempted they are accompanied usually by such pronounced non-specific irritation at the site of the injection as to preclude any possibility of increasing the injected doses to the point of clinical effect. Very few asthmatic conditions are due primarily to tobacco or pyrethrum, and in these the exposure is usually by way of inhalation of the fine dust-like particles. Horse serum, of course, is never used except for diagnostic purposes. Any attempt to lessen spontaneous serum sensitiveness by injection would be both futile and perilous. The extracts of silk and of goat and cow epithelia are rarely used by injection since asthmatic symptoms due to the inhalation of these excitants are infrequent.

For injection purposes, extracts of the following inhalants are employed, where pertinent:

Regularly Used:
Pollens
Dusts (Both stock and autogenous)
Orris
Epithelia (*a*) Chicken, duck, goose
(*b*) Dog, cat, horse, rabbit

Occasionally Used:
Silk
Molds, especially alternaria
Epithelia (goat, cow)

Seldom Used and Always with Caution:
Cottonseed
Kapok seed

The following table of increasing dosage is usually applicable for injection purposes for the above mentioned inhalant extracts. Dust extract is the exception, the schedule for which is described on page 123.

Dosage Interval	*Dosage in Protein Nitrogen Units*	
	Very Sensitive*	Moderately Sensitive†
Initial Injection	10 units	10 units
After five to ten days	20 “	20 “
“ “ “ “ “	40 “	40 “
“ “ “ “ “	60 “	70 “
“ “ “ “ “	80 “	100 “
“ “ “ “ “	100 “	200 “
“ “ “ “ “	200 “	400 “
“ “ “ “ “	400 “	700 “
“ “ “ “ “	700 “	1000 “
“ “ “ “ “	1000 “	1500 “
“ “ “ “ “	2000 “	2000 “
	and continue at this level	3000 “
		4000 “
		5000 “

* When the skin reaction is marked to a 100 unit test extract.

† When the skin reaction is moderate to a 100 unit and marked to a 1000 unit test extract.

The degree and extent of local reactions at the site of injections must be watched in order to anticipate and prevent constitutional reactions which may occur as discussed under the treatment of pollen allergies (Chapter 10).

In the very sensitive group the maximum dose may be only 400 to 500 units in some cases, while in others the doses may be increased to a maximum of 5000 units, which may be repeated once monthly as in the perennial method of pollen treatment. By using the quantitative methods of estimating dosage, discussed in Chapter 10 as applied to pollen therapy, gradually increasing amounts of the specific excitant can be given by subcutaneous injection at five- to ten-day intervals over a period of weeks or months until a relatively high dose is reached. For instance, a horse asthmatic who demonstrates a moderate reaction by intracutaneous test to a horse epithelium extract with 100 P.N. units per milliliter and a marked positive to 1000 P.N. units per milliliter should receive as his first dose an initial injection of 10 units. He may usually reach, by relatively easy stages, a top dose of 2000 to 5000 units; once achieved, the top dose may be repeated once monthly. Such extended treatment is desirable in those instances in which the excitant is unavoidable, as in the horse asthmatic who, finding it impossible to escape contact with horses, may elect to continue his maximum monthly dose of horse dander extract. Specific injections against several inhalant excitants may be given simultaneously, even though their dosage requirements may vary.

The unit method of estimating dosage cannot be applied to *dust extracts.* As discussed in the chapter on the preparation of extracts, it is not feasible to standardize dust extracts by their nitrogen content. The solution made by extracting an excess of dust is used in its concentrated form and in a 1:10 dilution. The schedule of doses begins with 0.1 ml. of the 1:10 dilution and increases by 0.1 ml. each week to a maximum dose of 0.5 ml. of the concentrated. Constitutional reactions rarely occur, unless the dust extract contains an unusually large content of another specific excitant to which the patient is sensitive. For instance, an extract prepared from dust obtained from a home containing a dog might easily produce a constitutional reaction upon injection in a person highly sensitive to dog.

The two principles, then, in the treatment of uncomplicated inhalant asthma are avoidance, when possible, of the air-borne excitant and specific immunization therapy.

FOOD. The only food extracts used for injection are those of the cereal group (wheat, rice, rye, corn) when these excitants, by inhalation, produce asthma in cooks, chefs, bakers, millers. The table of dosage previously suggested for the inhalants may be used (p. 122). The results are indifferent, often unsuccessful. Buckwheat, a highly potent antigen, should not be used for injection purposes.

In all cases of food allergy by ingestion, whether of the immediate type with the excitant demonstrable by skin test or of the delayed type with no skin reaction, the accepted form of treatment is by avoidance only. In occasional instances when an essential food is involved, such as egg, milk or wheat, immunization may be attempted orally or by injection. Extremely small initial doses must be given, and only modest increases attempted, since any patient for whom such therapy seems necessary is very highly sensitive. Indeed the indication for such treatment, the extreme sensitization, becomes a powerful contraindication to injection treatment. Many reported successes in food "desensitization" in children are due in reality to the fact that injection therapy happened to be given during the period when nature was correcting the condition. Spontaneous recovery from a food sensitization, though often slow, is a phenomenon frequently noted.

General Measures. *Education of the Patient.* No plan of allergic therapy is complete that does not provide for the proper education of the patient in the characteristics of his infirmity, list the requirements for successful treatment and emphasize the necessity for his cooperation. Patiently, and in detail, preferably in writing as a permanent record for the patient, the physician should explain the type of asthma as diagnosed and the significance of the identified antigens; give instructions for the avoidance of and for the escape from the indicated factors; and explain the form of treatment, with its usual attributes of frequency of injection therapy, its continuation often over extended periods of months and of years, and the possibility of occasional constitutional reactions. In the New York Post-Graduate Allergy Clinic, where there is pressure for time, a small illustrated booklet written for the lay person is furnished to each patient, together with instructions specific for his problem.

The patient with non-infective asthma should know that, although the excitants which produce his attacks are non-bacterial, the edema and congestion produced in the respiratory tissues may become so marked and so prolonged that a secondary invasion by bacteria may occur, which in turn, by its persistence and overwhelming character, may usurp the position of primary importance held by the air-borne inhalants. Sinus and bronchial infections appear in at least one half of all the cases of protracted inhalant asthma, often making or obscuring the initial symptoms, and becoming so severe in about one quarter of all the cases that the treatment must be directed not only against the inhalant or food factors, but against the infective as well. In brief, the plan of therapy in this group should include measures described in the chapter on bacterial asthma, as well as those given here. Every inhalant asthmatic is potentially an infective asthmatic, a likelihood which is greatly enhanced in the untreated case. No worse advice could be given to the patient than the suggestion that he ignore his symptoms. They may be "outgrown," but all too frequently they are "overgrown" by an infection which becomes implacable.

Therapeutic Measures. For the consideration of the therapeutic or symptomatic measures in non-infective asthma, the cases may be divided into those that experience acute attacks of varying severity but with freedom of symptoms between attacks, and those with chronic asthma who are never entirely clear. The emergency cases, the so-called status asthmaticus cases, rarely are found in the non-infective but rather in the infective group where they will be discussed.

The patients with acute isolated attacks usually develop symptoms which last from a few minutes to several days because of excessive exposure to their specific excitants, which are substances inhaled, such as pollens or horse dander, or ingested, such as egg. The attacks often are complicated by overexertion, emotional disturbance or lowered resistance from fatigue. A stay in the hospital, a journey from home, providing a sudden break with the usual environment is often the only procedure needed to end the attack. There are seldom secondary pathologic changes in these patients, so that the therapeutic measures may be directed largely against the increased capillary permeability and edema of the bronchial mucosa. Vasoconstrictor agents are therefore indicated.

In the mild cases *ephedrine* is the drug of choice. Related to epinephrine, chemically and physiologically, it stimulates the sympathetic nervous system, reducing edema of the bronchial mucosa by its peripheral vasoconstricting effect. Unlike epinephrine it is effective when administered orally. In children it may be given in the syrup of the National Formulary which contains 0.4 per cent ephedrine sulfate in ethyl alcohol, syrup of cherry and distilled water. Mild attacks may be checked by one teaspoonful, each one to three hours, for one or several doses. Codeine sulfate, 0.008 gm. to 0.015 gm. to the teaspoonful, helpful for the cough, may be incorporated in the syrup. In the adult, single or repeated doses of 0.03 gm. ephedrine may be sufficient. The unpleasant side effect of nervousness or insomnia caused by ephedrine and found chiefly in the adult is often quite marked and may be combated by the addition of an equal amount of phenobarbital for its sedative effect, though care must be taken to ascertain that the patient is not sensitive to this drug.

Epinephrine by parenteral injection is of course the ranking therapeutic agent in the severe acute cases. The dose is quite variable, depending not only upon the age of the patient and the intensity of the attack but also upon the individual responsiveness to the drug. No other medication in asthma requires more frequent adjustment in dosage than does epinephrine. The proper dose is that which produces as its side effects only mild tremor and mild pallor. In the adult as little as 0.1 ml. of the 1:1000 aqueous solution or as much as 1.0 ml. may be needed. If too low an estimate has been made, additional epinephrine may be given in five to fifteen minutes. This method is preferable to the administration of an overwhelming initial dose.

Epinephrine 1:500, incorporated in a slowly absorbed vehicle, either peanut oil[36] or gelatine,[37] to retard its effect, is occasionally indicated by hypodermic injection in non-infective asthma, in doses of from 0.33 to 1 ml. The use of the oil preparation in nut or seed-sensitive cases has seemed in rare instances to produce constitutional effects.[25]

Since gelatine is non-antigenic, epinephrine in this vehicle may be used in all types of food-sensitive patients.

Epinephrine, an aqueous solution 1:100, in the form of a spray by inhalation through the mouth is helpful in mild attacks, being used at intervals of from ten to fifteen minutes as necessary. A special nebulizer must be obtained for its administration. It should be used cautiously, never excessively or continuously and never in stronger solution than 1:100 since the desquamation of the tracheal epithelium may result with the loss of cilia.

Theophylline, a member of the xanthine group, used alone or in combination with ethylene diamine (aminophylline), is helpful in asthma in oral doses of 0.1 to 0.2 gm. which may be repeated each three to four hours. Aminophylline, 0.2 gm. in rectal suppositories of cocoa butter, is useful in children and, in somewhat larger doses of 0.36 gm., in many adults. The intravenous administration of the same drug is discussed under intractable infective asthma (p. 147).

Stramonium combined with nitrites is an old remedy but still useful, and in cigarette or powder form its penetrating, acrid fumes bring prompt relief upon inhalation.

Caffeine, another member of the xanthine group, usually employed in the form of black coffee, is useful in the mild attacks only. *Alcohol* is considered helpful in mild attacks.

Yet to be fully assayed are the advantages in the treatment of non-infective asthma offered by the newer antihistaminic drugs such as *pyribenzamine* and *benadryl* (beta-dimethyl-aminoethyl-benzhydryl-ether hydrochloride).

Codeine in 0.015 to 0.03 gm. doses orally is most helpful in combating the attacks of persistent cough which often accompany the asthma. It may be given every three to four hours or may be reserved for use at night in one to three doses, the first at bedtime for the disturbing cough which develops when the patient assumes a reclining posture. Codeine may be combined with routine injection of epinephrine, or given orally with ephedrine to produce relaxation and reduce apprehension in those who respond badly to the barbiturates. The narcotics, however, must be used with caution not only because of their habit-forming propensities but also because of their depressing effect on the respiratory center and upon the cough reflex. This is particularly true of morphine.

In the chronic asthmatic the symptoms become continuous. In the milder and earlier cases this may be due altogether to the influence of a factor which is removable and is subject to influence by specific treatment, as in the patient whose discomfort is due to the uninterrupted contact with the dog in the home or egg in the diet. In the more severe and more stubborn cases infective causes, primary or secondary, must be reckoned with. These produce hyperplasia of the mucosa and of the submucosa, hypertrophy of the mucous glands and of the bronchial musculature, and lead to emphysema, atelectasis and bronchiectasis. These irreversible conditions and the therapeutic measures indicated for them are discussed in the chapter upon infective asthma.

In the more persistent and severe non-infective cases fatigue must be avoided. In children, when fretfulness and nervousness are present, complete bed rest is often indicated.

Results of Treatment. The degree of benefit to be expected from specific treatment in the case of non-infective bronchial asthma will depend upon the ability of the investigator in identifying the primary antigenic factors, single or multiple; upon his success in interrupting their disturbing influence upon the patient; and upon the extent to which any secondary infective factors have produced a permanent stigma, rendering the condition irreversible.

In the simplest cases where the excitants are easily demonstrated by test, are easily removed from contact with the patient, and have been active so recently or so mildly as to encourage no secondary pathologic change, separation of patient and specific excitants produces a completely satisfactory result without the employment of any other corrective procedure. It must be borne in mind, however, that such a successful elimination of symptoms is not a cure, but simply a suppression of the manifestations of the allergic state. The asthma has only been deprived of its means of self-expression, as may easily be seen upon the reestablishment of contact between patient and the specific excitants, when all the original evidences of the sensitization will reappear.

If the excitants, though detected, cannot be entirely avoided, as in the case of purely non-infective asthma due to inhalants such as pollens, dusts and some animal danders, specific injection therapy is usually successful, the results being comparable to those obtained in the treatment of uncomplicated hay fever cases, relief from about 80 per cent of the discomfort being possible.

The results obtained in treatment in cases of food asthma with a delayed reaction time are good, provided the excitant can be detected and avoided. Due to the difficulties in diagnosing these cases, however, many go unrecognized.

In the cases of inhalant and food asthma which lose their non-infective status through secondary bacterial invasion, the outcome is often obscure. In such cases which possess the attributes of both the non-infective and the infective forms of asthma, the measures indicated in the former must be joined with those pertinent to the latter. Successful results become increasingly difficult to obtain, depending largely upon the ability of the physician to control the pathologic processes which involve more and more of the tissues of the respiratory tract.

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7. *Infective Asthma*
with
Pharmacopeia

ROBERT A. COOKE

Introduction

Doubts are occasionally expressed as to whether infection causes asthma, and if so whether infective asthma is allergy. The question is fair and deserves a considered answer. If asthma can be defined as a disease due to general bronchiolar obstruction, as I believe it can and should be, with dyspnea, cough and expectoration as the essential presenting evidences, then on the basis of symptomatology there is no reason to believe that asthma due to infection and asthma resulting from contact with inhalants (animal danders and pollens) or with foods may not both represent allergies to their respective causes. In addition, the physical signs, the antecedent and personal history of other allergies, the eosinophilia in blood and sputum, stamp the conditions as identical except as to the exciting cause and the immunologic factors involved. This is certainly true of asthma beginning in infancy and on to about forty years of age. Asthma starting after forty years does as a rule have special features which will be considered in greater detail, but there is nothing that stamps it as immunologically different from infective asthma of earlier years.

Infection as a Cause of Asthma. It is possible by the citation of a case to substantiate the position that infection of and by itself does cause the disease known as asthma. It is frequently seen by pediatricians and general practitioners and is without question so diagnosed and accepted. Some may prefer the term "asthmatic bronchitis" and to this no exception need be taken.

C. G., an infant of sixteen months, had had recurring mild upper respiratory infections with slight temperature and purulent nasal discharge. A few days after one such attack, coughing and wheezing began. Suddenly dyspnea set in and was very severe with cyanosis for several days. It could be temporarily controlled by epinephrine. The temperature rose to 102° F. and fell to normal by lysis after the third day. The leukocyte count was 15,000 with 8 per cent of eosinophils in the blood. A roentgenogram of the chest did not disclose any evidence of parenchymal consolidation. Physical signs in the chest were the typical sibilant sounds of asthma. Laryngeal cultures showed that the pneumococcus was the essential infecting organism. The mother had hay fever and the baby was very sensitive to egg which caused immediate vomiting with edema of the lips and tongue. This is a typical example of asthmatic bronchitis, but it is asthma and is due solely to the acute infection.

The essential point in these cases, as seen especially in infants and children, is the frequency with which one finds a substantial antecedent background as well as a personal history of allergy such as that to egg in the case cited. Following a few simple respiratory infections, the child suddenly becomes severely dyspneic with typical sibilant sounds and râles in the chest and fever. Leukocytosis and blood eosinophilia are usually present. A diagnosis of asthma or asthmatic bronchitis is made. Thereafter and for some years such a child usually has typical attacks of acute asthmatic dyspnea of several days' duration with frequently recurring respiratory infections. In the interval of weeks or months between attacks the chest is clear regardless of inhalant contacts or foods. This is an important differential point. Many such children as they grow older acquire other sensitizations, usually to dusts, danders or pollens, and asthma is frequent among these clinical manifestations. The fact is that infection may be the sole cause of many of the attacks of asthma.

Further evidence that infection causes asthma is obtained by the observed results of therapy based solely upon infection as the causative factor. In my opinion the prevention of recurring infections, both by removal of primary foci when they exist and by measures to combat and to resist infection, supplies additional evidence to permit the conclusion that infection is a responsible cause of the attacks of asthma.

Infective Asthma as an Allergy. The second part of the question is whether these attacks of dyspnea diagnosed as asthma and due to infection should be classed as allergies. The answer will be determined by one's concept of allergy. If the position is taken that allergy is based upon an immunology determined by the presence of an immediate wheal reaction on skin test then infection is not an allergy. With this narrow point of view I have disagreed (see p. 21). In the opening chapter it was brought out that clinical association of the various accepted allergies and an immunologic relationship based on an antigen-antibody reaction constitute a proper basis for an hypothesis of allergy even though the mechanism of the reaction in certain cases is not yet known.

However, in spite of this lack of a definite knowledge of the mechanism of bacterial allergy there are a number of good reasons for the assumption that infection, that is the bacteria themselves or their products, is a cause of an allergic response which may manifest itself as asthma alone or as one of several clinical expressions. These reasons may be enumerated as follows: (1) The familial background of allergy is particularly prominent in the acute infective asthma of infancy and early childhood. In a study which I made some years ago[1] there was a positive antecedent history of allergy in 82 per cent of the purely infective asthma cases with onset during the first ten years of life, whereas in those cases of non-infective asthma in the same age group which gave positive skin tests, the immediate wheal, an allergic lineage was disclosed in a somewhat lesser, 67 per cent, degree. In other words, the biologic capacity for sensitization transmitted by allergic antecedents and expressed in the offspring as asthma is similar for all types of asthma regardless of the cause, be it infection, foods or air-borne substance.

(2) The well marked association of infective asthma with asthma due to inhalants, drugs or foods, and with other allergies both past and present as hay fever, allergic dermatitis (eczema), urticaria and angioedema, stamps infective asthma as part and parcel of the entire allergy syndrome. Some years ago[2] a study of the causes of asthma in a group of patients of all ages showed that approximately 50 per cent of them had asthma due to inhalant, food or drug allergens, about 35 per cent had asthma due to infection alone and 15 to 20 per cent had asthma from both infective and non-infective causes.

(3) In asthma caused by infection alone, all other allergens as inhalants or foods being excluded, eosinophilia is present in the blood more frequently and to a greater degree than in those cases of asthma due solely to inhalant or food allergens. Eosinophilia is also present in the mucopurulent sputum or nasal discharge in practically all cases. Eosinophilic granulation is regarded as one expression of an allergic tissue response. (See Chapter 1.)

(4) The best and perhaps most convincing evidence of the allergic nature of infective asthma is the fact that a "symptomatic reaction" may frequently be elicited; by that I mean one may reproduce the asthmatic attack by means of small doses of vaccine, especially one made from an autogenous culture. In such instances the asthmatic response is a delayed reaction beginning twelve to forty-eight hours after an injection of the vaccine. It is not necessarily associated with any local reaction at the injection site and in typical cases is regularly induced by such minimal doses as 0.1 to 0.2 ml. of 1:1000 or 1:100 dilution of the standard 1.0 per cent by volume suspension of heat-killed bacteria.

This then is the essential evidence for a belief that asthma may be caused by infection with bacteria acting as antigens, or in other words it is a bacterial allergy. It is true that this belief is based largely upon asthma as it is seen in infants and young children for here the evidence is more clearly visible, but if the premise is sound that infection operates as an allergy in childhood there is little reason to question the further opinion that a bacterial sensitization may also exist as the foundation for asthma beginning later in life.

Incidence

Asthma is one of the common forms of allergy. There are no statistics that accurately tell the entire story, but there is some information such as that obtained by Vaughan[3] from the reports of the Army Medical Department for World War I when 2.45 per thousand were rated as asthmatic and rejected by the Draft Boards. Fifteen years later, however, there were twelve asthmatics per thousand among the veterans receiving compensation, in spite of the fact that more than two per thousand had previously been eliminated before induction. As there appears to be no sex difference, the general incidence of asthma would appear to be approximately 1 per cent in this entire age group (eighteen to thirty-five years). This incidence figure includes asthma from all causes and is not limited to any particular type or cause.

Etiology

Predisposing Causes.* One usually finds in the literature on asthma a long list of ascribed causes such as worry, excitement, psychic trauma and psychasthenia, vascular instability, autonomic imbalance, endocrine dyscrasia, exertion, fatigue, exposure to cold, dampness and irritating fumes and gases. If asthma, both infective and non-infective, is an allergy and only an allergy, as I believe, then the factors enumerated are not of basic importance. They may act as actual causes in so far as each or any of them predisposes to infection or possibly to sensitization and they may also function as non-specific causes. (See p. 135).

In World War I a number of soldiers were invalided after inhalation of the irritating mustard gas. Sulfur dioxide acts in the same way. Among the veterans many recovered, some had a continuing bronchitis and a small percentage became clinically asthmatic. Those examined had all the evidences of bronchial infection and some were found to have chronic hyperplastic sinusitis. Blood and sputum eosinophilia, the typical sibilant sounds in the chest and the response to epinephrine indicated the allergic nature and satisfied the requirements for a diagnosis of asthma. It may be properly assumed that the bronchial and pulmonary irritation predisposed to infections that were overcome in whole or in part. In the small group susceptible to sensitization a bacterial allergy developed. Occasionally this is seen in civil practice from sulfur dioxide fumes.

Other predisposing factors vary somewhat depending upon the age at the onset of the disease.

With onset before forty years of age: The important contributory factors are (1) Heredity as previously mentioned, especially in infants and young children. (2) Infections: (*a*) Acute specific infections of infancy and childhood, as pertussis, measles, scarlatina, pneumonia and influenza; or (*b*) acute pyogenic infections of the respiratory tract and ears; or (*c*) foci of chronic infection. These focal infections exist especially in the lymphoid tissue of tonsils, pharynx and nasopharynx in infants and young children. In older children and adults the sinuses also may be involved. All of these infective processes are factors for the promotion of bacterial allergy upon which the resulting asthma is based. (3) Other allergies of the wheal-reacting type such as perennial or seasonal coryza or asthma are likewise important in producing conditions which favor focal infection or acute bacterial invasion. These other allergies are not apt to be clinically active until the latter half of the first decade of life.

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*For a more complete discussion of this subject see Appendix page 547.

With onset after forty years of age: Asthma due to infection and beginning after forty years of age usually presents a somewhat different clinical picture. The primary cause generally resides in a focus of infection, usually in the upper respiratory and oral areas (sinuses, tonsils and teeth) and has existed for a variable period of years prior to the onset of asthma. Infection of the bronchial tract alone, however, is found in 10 to 15 per cent of the cases with no other discoverable focus. Occasionally asthma follows an acute pulmonary infection, as a pneumonitis, or there may be an exacerbation of a chronic focus which mediates the attack, but essentially in this age group the primary infection is focal, often asymptomatic and of long standing in contrast to the acute infectious processes of younger patients.

In general these cases do not have an antecedent or familial history of allergy and a history of other allergies past or present in the patients themselves is infrequent. They rarely give any immediate wheal reaction on skin test with inhalant or food allergens. However, in spite of all this there are certain facts that indicate the allergic nature and causal relationship of these foci to the asthmatic condition. First, these cases represent but a very small percentage of the genus *homo* and it seems a logical suggestion that the acquisition of sensitization in this older group depends in a measure upon some constitutional factor or fault or a combination of special circumstances permitting or favoring the development of sensitization. The situation is quite analogous to that seen in the contact dermatoses (see Chapter 13) and provokes the thought that hitherto latent hereditary forces may be operative in these as well as in the typical familial allergies of earlier years. Secondly, the allergic nature of the ensuing asthma is indicated by the histologic evidence of an allergic tissue reaction as eosinophilia in the primary focus as seen in the hyperplastic sinus membrane, and further by the frequency with which a symptomatic reaction (asthma) is elicited by vaccine injections, as mentioned. The clinical observation of Cooke and Grove[4] that these foci antedate the bronchial allergy by years indicates their causal significance rather than a concurrent relationship as suggested by many.

Specific Causes. As the name "infective asthma" implies, bacteria or viruses, or the products of both, are the actual cause. The organisms most frequently encountered and which may be proven allergens by resort to the "symptomatic" reaction are Diplococcus pneumoniae (all types), Staphylococcus aureus, Staphylococcus albus, Streptococcus (belonging to the hemolytic, viridans and indifferent groups), Hemophilus influenzae and Neisseria catarrhalis. Little is known of the viruses at present as far as asthma is concerned, but they appear to play a secondary or contributing rather than a primary role in the chronic cases though this point cannot be considered settled.

Non-specific Causes. In the section on predisposing causes (p. 133) I listed a number of factors which may predispose to asthma. These are often considered as direct causes of asthma. I do not consider them as such, but certainly they are frequently present in the asthmatic patient to modify the picture in important ways. They may appear to precipitate an attack in the asthmatic, they may even cause dyspnea, but they do not cause asthma (allergy). They must be recognized, eliminated or controlled if possible just as all other environmental and abnormal mental or physical conditions are, but true asthma infective or non-infective is not abated by treating them as primary factors.

Causes of Asthmatic Dyspnea. In asthma the dyspnea is due to inadequate pulmonary ventilation resulting from bronchial and bronchiolar obstruction. It is today generally accepted that blocking of the lumen of the smaller bronchi with tenacious mucofibrinous plugs is the chief cause as evidenced at autopsy. This is particularly the case in infective asthma. Edema of the wall is also present. In non-infective asthma of the wheal-reacting type due to pollens, danders or foods, a bronchial edema analogous to that seen in the nasal mucous membrane in hay fever is probable. The fact that nasal and bronchial lesions as well as edema of the skin (urticaria) coexist in systemic reactions due to therapeutic injections of allergens, and all respond equally well to epinephrine injections, indicates that edema is an important factor causing bronchial obstruction in non-infective asthma. In infective asthma edematous thickening of the entire wall is a regular autopsy finding.

The theory of obstruction by *bronchospasm* is an old one and still persists. It originated in the days when asthma was considered a neurosis or a simple nerve reflex and not an allergy. It received support from the observation of Auer and Lewis[5] in guinea pig anaphylaxis and it continues to be sustained by past and present pathologic reports of bronchial muscle hypertrophy. There is no direct evidence one way or the other, but there are some reasons to question the hypothesis of bronchospasm as the main cause of asthmatic dyspnea. Granted there is some hypertrophy of the muscle layer it is no greater in asthma than in chronic bronchitis in which the dyspnea of asthma is not a feature.

Some years ago I[2] compared the measurements of the several layers of the bronchiolar walls of varying sizes as reported by Huber and Koessler[6] in adults with asthma and chronic bronchitis. A survey of their work shows that the muscular hypertrophy is not as great in asthma as in chronic bronchitis. This is well illustrated in Table 19 which was made from their figures but rearranged for comparison. In the twelve sets of comparative measurements of bronchi varying from 0.5 to 12.0

TABLE 19

Comparative Measurements of Bronchi and Bronchioli in Adults with Asthma and Chronic Bronchitis

Patient	*Condition*	*Outside Diameter*	*Thickness in Millimeters*				*Gland (Diameter)*
			Wall	*Epithelial*	*Subepithelial*	*Muscle*	
Mr. E. L.	Asthma	0.50	0.12	0.033	0.023	0.019	....
Mr. Gr.	Bronchitis	0.50	0.14	0.013	0.020	0.033	....
Mrs. B.	Asthma	0.86	0.13	.....	0.014	0.014	....
Mr. Gr.	Bronchitis	0.88	0.11	.....	0.056	0.042	....
Miss L.	Asthma	1.80	0.35	0.050	0.050	0.033	....
Mr. A.	Bronchitis	1.80	0.44	.....	0.056	0.140	....
Mrs. B.	Asthma	2.40	0.70	.....	0.10	0.10	0.58
Mr. A.	Bronchitis	2.40	0.70	.....	0.12	0.18	0.28
Mrs. B.	Asthma	3.00	0.75	.....	0.070	0.070	0.88
Mr. A.	Bronchitis	3.00	0.77	.....	0.070	0.140	0.72
Mrs. B.	Asthma	4.64	0.92	.....	0.10	0.14	0.86
Mr. Gr.	Bronchitis	4.50	1.05	0.050	0.09	0.180	0.60
Mrs. B.	Asthma	5.76	1.68	.....	0.22	0.18	1.0
Mr. Gr.	Bronchitis	5.60	1.53	.....	0.20	0.2	0.71
Mrs. B.	Asthma	6.50	1.95	0.052	0.11	0.11	1.10
Mr. Gr.	Bronchitis	6.40	1.55	0.062	0.056	0.11	0.62
Miss L.	Asthma	7.50	2.25	0.056	0.140	0.240	1.0
Mr. Gr.	Bronchitis	7.50	1.65	0.056	0.070	0.180	0.71
Mr. G.	Asthma	9.00	2.25	0.071	0.12	0.090	0.72
Mr. Gr.	Bronchitis	9.20	2.50	.....	0.12	0.14	0.88
Mr. G.	Asthma	10.0	2.00	0.05	0.12	9.24	0.31
Mr. A.	Bronchitis	10.0	1.75	.....	0.20	0.19	0.88
Miss L.	Asthma	12.0	1.75	0.071	0.022	0.24	0.72
Mr. A.	Bronchitis	12.0	2.50	.....	0.2	0.35	0.88

TABLE 20

Comparative Measurements of Bronchi and Bronchioli in Infants with Asthma and Enteritis

Infant	*Condition*	*Outside Diameter*	*Thickness in Millimeters*	
			Muscle	*Gland*
A	Asthma	0.38	0.007	
N	Enteritis	0.38	0.010	
A	Asthma	0.92	0.010	
N	Enteritis	0.94	0.017	
A	Asthma	2.40	0.023	0.20
N	Enteritis	2.40	0.023	0.14
A	Asthma	2.64	0.019	0.36
N	Enteritis	2.68	0.013	0.28
A	Asthma	7.50	0.084	0.58
N	Enteritis	7.50	0.120	0.58

mm. in diameter, the entire wall is thicker in five of the asthma and six of the bronchitis measurements. In one set the measurements are alike.

No comparison can be made for the epithelial layer. There is nothing significant about the measurements of the subepithelial layer which is thicker five times in the asthma and five times in the bronchitis measurements, two sets having the same measurements. The muscular layer, however, is thicker in only two of the asthma against nine of the bronchitis measurements. This is in contrast to the glandular layer which is thicker in six of the nine asthma comparisons (all in the smaller bronchi) and in only three of the nine bronchitis (larger bronchi, 9–12 mm.) measurements compared. Even in infants the measurements given by the authors bear out this statement when asthma was compared with enteritis in similar sized bronchi as determined by the outside diameter (see Table 20).

Such data certainly give little ground for the general idea that smooth muscle hypertrophy in the bronchi is an outstanding condition in asthma, and affords proof that the dyspnea is due to bronchospasm. A comparison with normal bronchi as recorded by Kountze and Alexander[7] is not satisfactory, for it does not explain the relation of hypertrophy to dyspnea.

Further, there is no immunologic or sensitizing antibody mechanism for bronchial contraction in the naturally sensitive asthmatic man such as exists in the anaphylactic guinea pig. This is more patently true in the infective than in the non-infective asthma for no antibody of any kind has been demonstrated. Since the bronchial muscles definitely do not carry any antibody, it is difficult to see how histamine can produce bronchospasm, assuming that it is liberated in the type of allergic reaction under consideration (see Chapter 2).

Reflex action through the autonomic nervous system is another hypothesis that does not account for the symptomatic difference (dyspnea) between asthma and chronic bronchitis.

Finally, the failure of atropine to effect relief of asthma is a well substantiated experience and is a point against bronchospasm.

In short then, bronchiolar obstruction is due to mucous plugs, to inflammation and edema of the wall. These factors are definite. Muscular spasm as an added factor is very problematical and there is no concrete evidence of its existence nor, I believe, any necessity for assuming it to exist.

Pathologic Physiology and Anatomy

The pathologic findings in asthma must be considered in the light of etiology, the age of onset, duration and the cause of death, that is, whether the patient's demise was due to asphyxia of asthma, or whether the patient having asthma died of an acute intercurrent disease, as pneumonia, or an associated condition, as cardiac failure or emphysema. Certainly from recorded data available on many cases it cannot be stated exactly what was the cause of asthma during life nor for that matter the cause of death. In most asthmatic patients the terminal phases are protracted and death is due to the combination of bronchial plugging, emphysema, dilatation of the right side of the heart and exhaustion, with possibly an acute terminal pneumonic infection.

Infection is the essential and basic cause of existing asthma in the vast majority of patients who have died with asthma regardless of whether the terminal factors in death were attributed to related or unrelated acute or chronic disease. This has been my experience with patients from my clinic who have been carefully studied and diagnosed previously. An exception is made only in the uncommon cases who died from accident, allergic shock or from unrelated acute disease.

There is no question but that in patients who have had asthma up to the time of death there does exist as Rackemann[8] says, "findings which we have come to recognize as typical of asthma." This is what makes asthma, as I have said, a disease and not a symptom.

Aside from the lesions in the bronchi and bronchioles the pathologic findings divide themselves into (1) those resulting from prolonged dyspnea such as emphysema, (2) those conditioned by the constitution of the individual which we speak of as an allergic response, namely tissue eosinophilia and finally, (3) those common to all cases with prolonged chronic infection as for example the enlarged hilum glands and pulmonary fibrosis.

Lungs. Emphysema is present in all patients with asthma at the time of death. It is of greater or less extent and may not be of such grade as to be classed as anatomic or structural emphysema, but is none the less a factor in the symptomatology and gross pathology. This is well brought out in the Hurtado[9] studies which showed clearly that the degree of dyspnea was related to changes in pulmonary capacity and especially to the increase of residual air in relation to the total capacity. In the mild cases this ratio was 38.3 per cent while in the severely dyspneic it was increased to 72.5 per cent.

Parenchymal changes in the lung other than emphysema are not an integral part of asthma, but frequently occur and are observed at autopsy. In Rackemann's[8] series of fifty deaths due to asthma, eleven died of pneumonia. This was true particularly of those patients with onset of asthma before thirty who died between forty-five and fifty-five years of age. Pulmonary fibrosis is frequently seen in long-standing infective asthma, especially after forty years of age.

Mention must be made of the so-called Löffler's syndrome[10] not infrequently seen in asthmatic children and young adults, with transient pulmonary consolidation, fever, leukocytosis and eosinophilia of high degree.

Bronchi. The bronchi show thickened walls due chiefly to the marked increase in the glandular layer. The muscular layer is usually designated as thickened though not more than is often seen in chronic bronchitis. The basement membrane shows thickening and hyalinization. Eosinophile cells are abundant in the wall and the small and medium bronchi are filled with tenacious mucofibrinous plugs in which eosinophile cells are excessive. Thieme and Sheldon[11] emphasize sacculation of the bronchi as one of the important criteria for the pathologic diagnosis of asthma. It is not mentioned by others and certainly bronchiectasis is not a frequent clinical diagnosis in asthma. Hilum glands are enlarged as usually indicated by previous x-ray examinations.

Heart. While clinically there is often no evidence of cardiac failure even in severe asthma, there is no doubt but that the associated emphysema has exerted some effect. As expressed by Kountz et al.[12] "it appears that the heart is affected in the majority of patients with emphysema." This is supported by the findings of Hurtado et al[9] in asthma and emphysema. In the twenty-six cases observed there was electrocardiographic evidence of myocardial change in eleven of sixteen patients on whom readings were taken.

Cor pulmonale is one of the more common autopsy findings. In an excellent study on fifty cases made recently by Rackemann[8] cor pulmonale was the cause of death in five cases and was present in twelve of them. It is interesting to note that he records it as present in but one of the cases with asthma beginning after forty years of age. In seven of his cases with this right ventricular lesion asthma began before thirty years of age and lasted at least twenty years. Anatomic emphysema was not recorded in any of these. This is difficult to understand. Perhaps dyspnea over the years is a more potent factor than obstruction in the pulmonary circuit due to emphysema. In asthmatic dyspnea an increased negative intrathoracic pressure is produced by the rapid and violent inspiratory phase which sucks quickly into the right ventricle an excessive volume of blood dammed back in the vena cava during the prolonged expiratory period. It does not seem possible at this time to explain satisfactorily the lesion of the right side of the heart in all cases. Certainly it must be regarded as a response to increased work over a considerable period of years. In but two of Rackemann's[8] cases was there less than five years' duration of asthma recorded.

Blood. Eosinophilia is frequent in allergies as discussed in Chapter 1. It is more common and is of higher degree in asthma of infective origin than in that due to foods, inhalants or drugs, even when these are long-lasting. As previously reported in thirty-one consecutive cases of purely infective asthma, the percentage of eosinophils in the blood was over 5 per cent in nineteen cases, nine of these being over 8 per cent with a maximum of 27 per cent.

Sinus Disease. Hyperplastic sinusitis is a frequent precursor of bacterial asthma as reported by Cooke and Grove.[4] In autopsy as well as in clinical reports the presence or absence of sinusitis is rarely mentioned. The tissue change is entirely analogous to that of the bronchial mucous membrane and for reasons mentioned elsewhere is regarded as an allergic tissue response to infection and to infection alone and never the result of allergies to foods or inhaled substances. Eosinophilic infiltration of the membrane is the characteristic evidence of allergy.

Symptomatology

The symptoms of asthma are dyspnea, wheezing, cough and expectoration, which vary as does the clinical picture of the disease itself both in severity and duration and depending upon the age of the patient.

In Infancy. The attack of asthma usually starts with abruptness and severity, following a day or two of a mild respiratory infection. Breathing is labored and rapid with cyanosis dependent upon the degree of respiratory obstruction. The picture often is a truly alarming one and the wonder is that these little patients survive the several days of the attack. In the absence of special conditions such as thymic enlargement they rarely die. Waldbolt[13] and others have recorded a few deaths. Usually there is a fever of moderate grade, leukocytosis and blood eosinophilia. The attacks are more apt to occur in winter and recur at intervals of a few weeks or months. Between attacks, especially in the early stages, there is complete freedom from signs or symptoms in the chest though many of the infants do have continuous snuffles and may be mouth breathers. Allergic dermatitis or food allergies unrelated to asthma are not uncommon. Infective asthma in infancy, like infantile eczema, may tend to spontaneous recovery, but only after a period of years and after considerable damage has been done. An allergy is very apt to recur before puberty as asthma or some other non-infective allergy.

In Childhood. Infective asthma may begin between three years of age and puberty, but practically it is an extension from infancy and usually follows an acute respiratory infection. It is not so violent as in infancy and is more prolonged, even chronic, but the signs and symptoms are essentially the same. These cases are more than likely to be complicated by or, more accurately, they are likely to complicate, non-infective allergy such as asthma from inhalant allergens or seasonal or perennial coryza. The temperature often shows but little elevation, the leukocyte count may be normal, but blood eosinophilia is usually present. It is in this group that one is most likely to see children with marked chest deformity—pigeon breast—when asthma has been prolonged and is accompanied by obstruction to normal breathing from enlarged tonsils and adenoids. In the absence of adenoids and tonsils asthmatic dyspnea rarely if ever produces pigeon breast. The asthma may be mildly continuous but with frequent exacerbations or may be intermittent and paroxysmal and is accentuated by physical effort, fatigue and exposure to cold.

In Adults. In the age group from puberty to forty years of age many of the patients with infective asthma are but a continuation from the previous age groups with attacks occasionally of purely infective origin, but frequently combined with those from non-infective causes. The attacks may be strictly paroxysmal, but the general tendency is to assume a subacute or persistent course with occasional exacerbations of extreme severity for which there are several causes, such as an acute capillary bronchitis or pneumonitis or the sudden plugging of a bronchus with resulting atelectatic consolidation and pleuritis. In the older patients of this group one frequently sees definite evidences of hyperplastic sinusitis as a causative factor in the persistent asthma. The earlier sinusitis and polyposis appear, as for example between twenty and thirty years of age, the more unfavorable is the prognosis. The longer the attacks are allowed to continue the more extensive are the secondary changes in the bronchial, hilar and pulmonary areas; emphysema is slowly increased, the vital capacity is much reduced and the patient's activities are gradually and increasingly limited.

Asthma after Forty Years of Age. Some of these cases too are merely continuations of asthma from the previous age groups, for there are many patients with mild and occasional attacks of asthma through a lifetime of sixty to seventy years or more. There is a great deal of truth in the saying "once an asthmatic always an asthmatic." In all these patients, whatever may have been the cause in earlier life, as age advances the infective element steadily gains the upper hand as the effective etiologic factor, while inhalant non-infective causes gradually assume an insignificant role.

It is the cases with onset of asthma after forty years of age that are of particular concern because of the doubts expressed by some as to whether they are allergies and even whether they should be called asthma. This was considered in the introductory discussion (see p. 131). Usually there is a negative antecedent history of allergy, often no past history of allergy or if present it is vague, distant and does not involve the bronchi. The intradermal skin tests are quite uniformly negative, but if positive they cannot be causally related to the asthmatic attacks.

There are several types of cases. (1) The onset of asthma is abrupt and severe. A typical example is that of a patient seventy years of age who had had hay fever some years before and responded to pollen therapy. While worried over his wife's health and fatigued by attention to her care, he was suddenly taken with attacks of severe dyspnea with nocturnal exacerbations. He was admitted to the hospital on the third day of illness when the wheezing, dyspnea and sibilant sounds in the chest were typical of asthma. There was no clinical evidence of cardiac failure and the electrocardiogram was normal. His temperature was 101° F., pulse rate 100, blood pressure 140/90, urine normal, eosinophile cells were abundant in the mucopurulent sputum and reached a total of 5 per cent in the blood. This was an excellent opportunity for a diagnosis of "neurogenous" asthma. A roentgenogram of the chest showed an area of consolidation in the lower lobe of the right lung near the hilum. Under sulfadiazine therapy he made a rapid recovery with complete resolution of the consolidation after ten days. Diagnosis was lobar pneumonia and asthma.

(2) The onset of asthma (dyspnea) may be abrupt, but it follows a long history of nasal difficulty such as obstruction, sneezing and discharge. Not infrequently nasal operations as polypectomies, antrotomies and septum resections for the relief of nasal obstruction and sinusitis have been done. Many of these patients have a history of cough over a period of years and occasional attacks of bronchitis, but never the symptom of dyspnea nor the signs of asthma. Quite suddenly and following an acute infection, typical asthmatic dyspnea begins and from then on these patients become increasingly asthmatic with periods of freedom becoming shorter and less frequent. They ultimately develop a persistent asthma of steadily but slowly mounting intensity.

(3) Another type is that in which there is over a period of years a slowly progressive dyspnea with cough, wheezing and expectoration. Finally comes the time at fifty or sixty years of age when self-medication with asthma cures for symptomatic relief fails to give satisfactory results. These patients are apt to be thin almost to the point of emaciation, the chest may be barrel-shaped and expanded or it may be small and the costal cartilages calcified. The important point is that the expansion is poor and the vital capacity markedly reduced. These are the cases about which most doubt arises as to whether or not they should be called asthma and whether they are allergies at all. It is a situation which calls for diagnostic acumen. Some have pulmonary fibrosis and emphysema. They are not cases of asthma, they have none of the stigmata of allergy and they are not relieved by epinephrine and other anti-asthmatic medication. But there is no doubt of the diagnosis in the majority in whom primary foci of chronic infection are found in sinuses, tonsils or teeth when carefully examined. The sibilant sounds in the chest are typical and eosinophilia is marked in the blood, in the sputum and in sinus membranes removed at operation. It is true that this is not the picture of asthma beginning in early life, but it is the same type of bronchiolar obstruction necessarily modified by the secondary changes induced in the bronchial and pulmonary area after years of absorption from a chronic infection of the upper respiratory tract of which the patient may have been entirely unaware.

This then is the average and varied picture of asthma beginning in the various age groups and developing or extending over the span of years. Of course, the lines of distinction between age groups cannot be drawn too hard and fast, but in general this description is applicable to the great majority of cases of asthma I have studied.

Complications

In infective asthma complicating diseases are common. In children otitis media, mastoiditis, pyelitis and retroperitoneal adenitis and cyclic vomiting are met with in addition to allergies other than asthma, especially dermatitis and hay fever. In adults and the aged acute infections as pneumonia and chronic systemic diseases as arthritis, diabetes, hypertension, vascular and renal disease, in addition to the usual sequelae such as emphysema and pulmonary fibrosis—one or another of these is frequent. Hyperthyroidism, pre- or postoperative, is not rare and is a serious complication of adult asthma, the thyroid condition having antedated the onset of asthma as a rule. Hypothyroidism of mild degree is not uncommon. I have never seen a case in which asthma was modified by the use of thyroid medication. In my experience true and demonstrable bronchiectasis is rare. It cannot be diagnosed from any roentgenogram unless lipiodol has been used.

Diagnosis

This consists of two parts. A diagnosis of asthma must first be made and then one must determine the cause or causes, for there may be several. To be accurate the differential and etiologic diagnosis must be based upon the data obtained through a careful history, complete physical examination, certain necessary laboratory data and lastly, skin tests properly done and interpreted.

The outline for a proper diagnostic examination of the presumed allergic case (see p. 37) should be used in so far as it applies to asthma cases. Actually the diagnosis of asthma is not too difficult as a rule, but if the physician is to outline or conduct the management and treatment of the case he must study and know his patient, mentally and physically. He must be informed on all illnesses, related or unrelated, and on the normal or abnormal functioning of the various systems such as the respiratory, circulatory, digestive and excretory.

Among the important observations leading to a diagnosis of asthma in patients with cough, dyspnea and expectoration are an antecedent history of allergy, other allergies in the patient whether present or past, the presence or absence of positive skin tests and an increase of eosinophilic leukocytes in the blood, sputum or nasal discharge. The presence of blood eosinophilia over 8 per cent is truly indicative of an infective cause as such counts are rarely seen in non-infective allergy.

On physical examination if asthma be present at the time, *sibilant* *sounds* are heard in the chest. If the examination is made during an interim physical signs may be absent. I should like to emphasize this characteristic sign. Sibilant sounds are not at all like mucous or subcrepitant râles, but are smooth high-pitched musical notes created by the passage of air under pressure through or past the obstruction in the small bronchi. The physical factors involved are quite like those that produce a whistling sound. Often they are elicited only on forcible and complete expiration and in mild cases may be missed unless carefully listened for with this technic. The sibilant sound when scattered over the chest is as nearly pathognomonic of asthma as any sign can ever be. It does not occur in bronchitis, acute or chronic, nor in penumonia, nor in congestive heart failure and is not present when tumors or foreign bodies obstruct the trachea or bronchi. Its presence is significant evidence of asthma.

As I have said, the diagnosis of asthma during its active stage is not as a rule very hard to make, but the diagnosis of the existence of the asthmatic state or asthmatic predisposition is by no means easy. The difficulties have been brought home during the recent war, in the problem of a correct diagnosis among selectees for the armed forces. If the draftee is anxious for service, conceals a history of past asthma and is free with chest clear at the time of examination, a diagnosis of presumptive asthma, that is, an asthmatic allergic state, is not possible and would not be suspected. If asthma be present the diagnosis should be made, but when a statement has been given of previous asthma then careful scrutiny may disclose the probable truth or falsity of the statement. It is important to remember the general age group of the cases here to be discussed. In asthma of the draft age group antecedent allergy is found more frequently than not and other allergies of the skin-reacting type are frequently associated. The history of past asthma and other allergies, together with antecedent allergies, should be obtainable and of course supported by properly sworn statements of physicians previously consulted and other responsible citizens. Physical examination of the chest during deep inspiration and forcible expiration especially after severe exertion may disclose evidence of sibilant sounds if attacks have been at all recent. Blood eosinophilia over 5 per cent is presumptive evidence of latent allergy. Skin tests with a few of the more important allergens if definitely positive and confirmed are indicative, not necessarily of the cause, but of an allergic state, and are, therefore, significant.

Attention to these few points would have helped to exclude many who were accepted and became serious liabilities. The necessity for some such measure of diagnostic technic is becoming more and more evident.

Differential Diagnosis. All dyspnea is not asthma. Hence differential diagnosis must always be applied to rule out such conditions as renal and cardiac dyspnea, tumors of lung and bronchi, foreign bodies, tuberculosis, pulmonary fibrosis, silicosis and pleural effusion. Of help in this regard are roentgenograms of the chest with and without lipiodol in the bronchi, blood pressure, urine analysis, blood counts and blood chemistry, bronchoscopic examinations, electrocardiograms, venous pressure and circulation time (see Chapter 8).

With the data assembled from the history, physical examination and such clinical laboratory procedures as the case may indicate, the physician usually is able to approve or deny the existence of asthma; in fact he should be able to make a correct diagnosis of any existing cause of dyspnea.

Etiologic Diagnosis. The next step, if the disease be asthma, is to proceed to a diagnosis of the cause. This takes time, care, patience and experience. It is important because on this rests the success or failure of the management of the case. No one cause but all causes, infective and non-infective, must be ferreted out. The negative as well as the positive findings are of value in the complete study.

To differentiate non-infective and infective asthma is sometimes difficult and resort must be had to such clinical tests as environmental change to eliminate air-borne factors as well as restrictive diets to rule out food allergens. Hospitalization for five to seven days with resulting rapid improvement in asthma helps establish the relative importance of inhalant causes. If a food allergen is eliminated for the same period a rapid disappearance of symptoms will likewise result. In other words, allergens do not continue to operate many days after their complete withdrawal. Occasionally the differentiation of causes in some of these cases is extremely baffling. This is true especially in children. They are much better in the hospital, but the signs in the chest persist. Such cases often turn out to be examples of combined inhalant (domiciliary) and infective asthma.

Focal Infection. In making the diagnosis of infective asthma the history of the attacks, their frequency, course and duration, as well as antecedent conditions are all of importance. Preceding "colds," fever and leukocytosis are usually indicative of an infective process. An eosinophilia over 8 per cent is rarely seen except with infective allergy. With recurring attacks of asthma foci of infection should be sought. If by the process of elimination, air-borne, food and drug allergens are ruled out, the one known and important factor remaining is infection and the existence of foci of infection, especially in the upper respiratory area, makes them not only possible but probable causes. In the physical examination, which must be complete, the physician should be able to and should use the nasal speculum and pharyngoscope and employ roentgenograms of the sinuses in these examinations or he must have recourse to a competent rhinologist, as important nasal foci will otherwise be and often are overlooked.

The same is true for *dental infections*, especially those in the subantral areas. Of interest in this connection is the case of H. F. whom I saw over twenty years ago. Then aged sixty, he had a story of mild but steadily progressive asthma for two years. There was evidence of right antral sinusitis and roentgenograms showed clouding and a peculiar shadow of a foreign body in the antrum. Foul-smelling pus was obtained from the antrum irrigation. A non-vital bicuspid tooth underlay the antrum. This was extracted. One day the foreign body, a piece of gutta-percha filling three-quarters of an inch long, was recovered, having been washed through the natural antral orifice. It was a piece of the root canal filling from the tooth. The antrum promptly ceased discharging. The asthma cleared in a few months and the patient, now over eighty years old, has had no asthma since that time. The right antrum is now as clear as the left on transillumination.

This case not only illustrates dramatically the importance of dental sources of infection, but substantiates the thesis which I maintain, namely, the causal relationship of sinus infection and infective asthma.

Treatment

It is of course essential that whenever infective and non-infective causes are present, both must receive treatment at the same time. See the Pharmacopeia of Asthma (p. 159) for specific information regarding the drugs mentioned in this section.

Symptomatic Therapy. This is directed principally to the relief of dyspnea and cough, both of which if uncontrolled tend to increase and prolong the asthmatic attack. The conscientious physician does not continually prescribe symptomatic therapy except to those patients who have been carefully studied for an etiologic diagnosis, or as a preliminary to such a study. In infective asthma the symptoms may be mild though prolonged, or they may appear in varying grades of severity either as exacerbations or as intermittent acute paroxysms.

For *mild asthma*, consisting of wheezing and an uncomfortable dyspnea or sense of chest pressure, many patients secure adequate comfort from the use of ephedrine alone, or in its several prescriptions which include sedatives to neutralize the nervousness and wakefulness resulting from its use. When taken at bedtime it may give a comfortable night, especially if enteric coated ephedrine is also taken to prolong the effect. The stronger epinephrine (1:100) by inhalation for occasional use, or aminophylline in tablet form or as a suppository or enema may serve as well. Occasionally patients find great relief from aspirin. It must be prescribed with great care and only to those who know they have used it safely. In infective asthma it is particularly dangerous as sensitization is not uncommon and death in asphyxia has followed within one-half hour after 5 grains by mouth. Potassium iodide or hydriodic acid taken for several days or weeks should be given a trial. Asthma powders or cigarettes for inhalation are available commercially. The recent types of antihistaminic drugs have not yet been adequately evaluated. The two now being used clinically, pyribenzamine and benadryl, have not been particularly effective in controlling the asthmatic dyspnea even temporarily.

In cases with *moderate asthma*, epinephrine (1:1000) in water or in oil may be used subcutaneously in addition to the measures mentioned above, the former for quick effect and the latter for more continuous effect. Cough may be a symptom that requires control and for this purpose one may try the anesthetic lozenges (Nuporal), but codeine is the drug par excellence, either by mouth as a tablet or preferably in an elixir with terpin hydrate. Occasionally a subcutaneous injection is required. In children benzoin steam inhalations may help.

Severe asthma in short paroxysms or long continued (known as status asthmaticus) is a real test of therapeutic skill. When possible these patients are more competently treated if hospitalized. Epinephrine (1:1000) subcutaneously must be used and sometimes frequently repeated. The 1:100 solution for inhalation should be tried. The preparation in peanut oil may be used by injection at least twice a day along with the watery solution. For those unable to take this oil on account of severe local reactions epinephrine in gelatin is useful. At times these patients in status asthmaticus are said to become "epinephrine fast." This is not a suitable term for there is no proof that epinephrine fails to act, only that it fails to relieve dyspnea when the bronchial plugs cannot be dislodged.

Aminophylline by intravenous injection may be more effective than epinephrine. This may also be given by intramuscular injection, by suppository or in a small water enema for retention. When taken by mouth it is apt to cause nausea. It may be given intravenously twice or even four times a day when the situation is critical and double the usual dose may be tried. It should always be given slowly at the rate of 1 ml. per minute for best effects.

Digitalis, strophanthin or coramine should be used in those in whom cardiac failure is indicated by signs of pulmonary congestion, enlarged and tender liver or subcutaneous edema, or by alterations of venous pressure, circulation time or electrocardiograms. Dyspnea is of course accentuated by any degree of circulatory congestion.

One of the objects of therapy is to facilitate respiration by clearing the bronchioles, and for this purpose iodides may be a help as they stimulate a mucous secretion which tends to loosen the bronchial plugs. Care must be taken to avoid iodides in those allergic to them. Sodium iodide may be given intravenously once or twice a day, alone or combined with aminophylline, but only after it, or the potassium salt, has been given by mouth and found not to be a cause of allergic edema. Ipecac, to the point of emesis, is an old-fashioned remedy too often neglected but it serves a very useful purpose, especially in children though I have used it effectively in adults, in attaining some of the purposes of our therapy. There is nothing to compare with the act of vomiting for dislodging the bronchial plugs. Ammonium chloride and other expectorants may be tried. Atropine and belladonna are mentioned here only to be condemned as they effect a result diametrically opposed to that sought, as they increase the bronchial obstruction by drying the secretion. Their action to relieve bronchospasm, if it exists, does not compensate for the detrimental effects noted.

Sedation. There are many who believe that opium and its derivatives should never be used in asthma. I do not concur. Such sedation must be given carefully and in doses to control cough and allay distress but not in amounts sufficient either to slow respiration appreciably, to stop cough, or do more than produce the mildest relaxation. If vomiting results so much the better. Of course care must be exercised in their prolonged use on account of the danger of habit formation. In the majority of cases I prefer pantopon or codeine by injection. For children and infants codeine suppositories are very satisfactory. For gentle sedation and for sleeplessness the barbiturates, bromide, chloral, or paraldehyde may be used.

Every physician becomes accustomed to the use of one or several of the drugs listed as sedatives in the pharmacopeia and there is no striking advantage of one over another. However, in cases of long duration a change may be indicated from time to time. Also allergies to certain drugs do exist, and I have encountered a definite asthmatic allergy to one barbital compound which did not extend to all of them, but in general if one suspects such a sensitization it is better to change to some drug not in the barbiturate series.

Other Measures. Oxygen alone or combined with 20 per cent helium is comforting to most patients with dyspnea especially when cyanosis is present, and it may be used continuously when dyspnea persists. Since asthma patients as a rule object to facial masks and even the tent, the cost of helium is almost prohibitive. Practically, oxygen alone is entirely satisfactory and is easily administered by metal catheters or small rubber catheters well lubricated, inserted along the floor not up the nose and with the tip about halfway to the pharynx. The pressure tank of oxygen may be used instead of the hand bulb when attached to the special nebulizers for epinephrine, or even for penicillin if one or both are being used for inhalation therapy.

Hyperpyrexia has been used to help break up a severe prolonged and resistant attack of status asthmaticus. It is based upon the observed fact that an intercurrent febrile infection such as pneumonia does that very thing. My preference of means to produce artificial fever, because it is the simplest, is the intravenous injection of typhoid vaccine. The standard triple typhoid vaccine is diluted ten times with sterile saline solution. The aim is to stimulate a rise in temperature to 102°—104° F. and this may be accomplished with 0.1—0.2 ml. of the diluted vaccine. If no reaction occurs within two hours a dose of 0.5 ml. should be given. One ought never to use the concentrated vaccine as it may produce serious vasomotor collapse. This vaccine reaction is often helpful for these patients in status asthmaticus and well worth a trial; while the effect is temporary just as in intercurrent pneumonia it may afford the patient a welcomed respite.

Diuresis may be indicated in the severe cases not dehydrated by lack of fluid intake or vomiting. An insensible edema may exist, and if the tissues of the bronchi are involved this will increase the dyspnea. Attempts may be made in selected cases to relieve edema by promoting diuresis as well as by catharsis. The caffeine and theophylline drugs may be used, or mercupurin may be given intravenously. It is more effective when preceded by several days' medication of ammonium chloride given by mouth. Stoesser[14] finds value in the administration of potassium chloride. Glucose or sucrose in 50 per cent solutions, as suggested by Keeney,[15] given in 100 ml. amounts preferably with small amounts of 0.2 ml. epinephrine (1:1000) promotes diuresis and occasionally helps.

During the severe stage of dyspnea if fluids are not taken or vomiting occurs, 5 per cent *glucose* in saline solution should be used intravenously or by clysis and repeated as indicated. One should always be on the alert for the need of fluids on account of the fluid loss by sweat and through the breath in the severely dyspneic patient.

Steam inhalations with or without benzoin may be useful in some cases, especially in children with acute infections. Mustard paste broadly applied to the front and back of the chest for short periods several times a day may help to relieve the pulmonary congestion, but is more welcomed for the effect it seems to have on the aching muscles of respiration.

Finally and as important as any of the other measures is the attention to the *gastro-intestinal tract* and to the *feeding*. Abdominal distention even of slight degree accentuates the respiratory distress from pressure on the diaphragm. The treatment of all severe cases should begin with thorough catharsis, such as two compound cathartic pills at night and a full dose of magnesium sulfate in the morning. Throughout the attack laxatives or stronger cathartics may be necessary, as well as enemas or high colonic irrigations. The diet during the attack must be light for a few days, often nothing but fluids as fruit juices, broth, gruels, weak tea or coffee with sugar and water, when dyspnea is severe, but gradually enlarged to soft and solid food as dyspnea lessens.

In cases of prolonged status asthmaticus when dehydration exists and anorexia makes feeding impossible, resort should be made to intravenous administration of essential amino acids. Prolonged protein deficiency favors a vicious cycle of exhaustion and anorexia which may be corrected by this modern type of therapy. Amigen or any of the other commercial preparations in amounts of one liter twice a day, and preferably with 5 per cent glucose, may bring spectacular results in those patients dying from starvation as much as from asthma. Several commercial preparations are now available and oral therapy will undoubtedly be procurable shortly.

Etiologic Therapy. Having completed the study and determined the cause or causes of asthma in the particular case, the next step is the treatment directed against the cause, which for the present purposes of this chapter is an infective one. However, it must be remembered that all inhalant and food factors are likewise and at the same time receiving proper attention if they too are genuine causes. With regard to the infection such general procedures are available as antibacterial chemo- and immunotherapy, the removal of the foci of infection, the prevention of recurrences and the general management of the patient.

Antibacterial Chemotherapy. Within the past few years there have come into use powerful bactericidal and bacteriostatic drugs which serve a definite purpose in the treatment of infective asthma. I have reference to the sulfa compounds and penicillin. The sulfa drugs, especially sulfadiazine, are useful in the acute phases of infection causing asthma. *Sulfadiazine* may be used in any and all such cases from infancy to old age when infection is caused by bacteria affected by the drug. Sputum cultures, or laryngeal in case of infants, are therefore indicated early in the infection and since many infections are due to the pneumococcus, streptococcus or staphylococcus, therapy may be started as soon as cultures are taken. In the presence of an acute infection or exacerbation the drug should be prescribed in full doses for at least a week and continued in protective doses for at least two weeks longer. All the precautions that attend its use in internal medicine are to be observed. It should be given with bicarbonate of soda and attention paid to fluid intake. Checks on the blood count, hemoglobin and urine should be made at least weekly. In chronic infections I have used the drug in small doses, as 1 or 2 gm. a day, over periods of several weeks to several months with apparently satisfactory results in a good percentage of properly selected cases when necessary precautions could be observed. Sensitization to sulfa drugs does occur in these allergic cases, but no more often than in general medical practice. It must be watched for. The evidences of sensitization or toxicity are fever, anemia, leukopenia, urticaria, dermatitis, simple erythema and renal irritation. I have seen but one case in which asthma could be attributed to its use. In a few of my cases the allergic reaction has been severe with general erythema and acute enteritis. In one of these the reaction developed within twenty minutes. The application of sodium sulfadiazine to the unbroken skin produced an immediate wheal reaction. This is the only case I have seen in which the sensitivity was transferable to normal skin.

Penicillin therapy in infective asthma is still new, but the indications[16, 17] are that it may be useful in certain cases. Our[17] present series of over sixty cases has not been observed long, one year at best. Certainly it is not effective in all cases and is no general panacea. Hampton et al.[16] have reported on its use in nine cases without benefit. Whether results depend upon the sensitiveness of the infecting organism to the antibiotic drug remains to be seen. One case of urticaria and one case of urticaria followed by asthma have been observed by me following its use. In the former case passive transfer of the sensitizing antibody was not effected. Seemingly the drug is peculiarly non-toxic when used in average doses of 100,000 units a day though various sensitization phenomena have been reported, especially in cases of syphilis receiving large doses. Urticaria and dermatitis are the usual clinical evidences of sensitization and asthma has been noted. In general in my cases, the drug has been used by intramuscular injections of a saline solution in doses averaging 100,000 units a day for ten days. Penicillin by inhalation is being tried, as is oral therapy. It is too early to evaluate its effects, but in general, when focal infection exists the benefits if any are apt to be temporary. Its usefulness lies largely in the control of the acute stage of upper and lower respiratory infections.

Immunotherapy. Vaccine therapy is a two-edged sword to be used with caution in any allergy and especially in asthma. It is based upon empiricism and experience because our immunologic and bacteriologic knowledge is limited. There are no laboratory tests to warn or guide one. In the absence of information on bacterial specificities it is most reasonable to expect a specific effect from a vaccine prepared from autogenous cultures. In my clinic I use vaccines prepared from cultures of sputum, from sinus washings or from cultures of tissues removed at operation. The vaccines generally include several organisms which are killed by heat and combined in equal parts in a basic 1 per cent by volume suspension. It is safer to start with high dilutions such as a 1:1000 dilution of the 1 per cent suspension, gradually and slowly increasing by weekly doses to perhaps 0.5 cc. of a 0.1 per cent suspension. If reactions are met with or even suspected, the dose is lessened or temporarily omitted.

Actually the best results occur in those patients in whom a symptomatic response (asthma) is elicited with very small doses. These reactions are delayed for twelve to forty-eight hours. Skin tests with vaccines offer no clues and no help. Treatment is continued over a period of months by means of gradually increased weekly doses up to the maximum desired and such injections are then given indefinitely every two to four weeks. Overdosage is the great danger. I have seen patients kept in status asthmaticus merely by vaccine injections. The results are occasionally surprisingly satisfactory, but on the whole they are not dependable and these treatments should be regarded as adjuvants for prevention of recurrences after removal of focal infection.

Management of Foci of Infection. In infants and young children the foci are practically limited to the lymphatic tissue of the upper respiratory tract. Tonsils and adenoids when infected should be removed as early as it is possible to secure favorable conditions. The adenoid and tonsil operation may properly be done at two years of age on the predisposed or actually allergic children. It should not be done within six weeks after an acute infection nor during any epidemic such as poliomyelitis. A tonsillectomy should command all the respect of a major operation though unfortunately it often does not. Since nearly one half of these operations on patients from my clinic at the Roosevelt Hospital are secondary, the general operative work cannot be judged as very skillful. However, when competently done and with all precautions, there is no procedure that yields better results. Grove and I together have watched these cases over the past fourteen years [4, 18, 19] and among the hundreds of operations he has performed I have never yet seen asthma develop as a result of operation. We have convinced ourselves also that lymphoid hyperplasia of the pharynx does not result from the early and complete removal of faucial and lingual tonsils and adenoids, but from continuing infection when the operation is imperfectly and incompletely done. It is infection in the remnants that stimulates lymphoid overgrowth.

ROENTGEN AND RADIUM THERAPY. When infected lymphoid tissue exists on the pharyngeal wall and is not susceptible to surgical removal, the most satisfactory procedure is the use of roentgen or radium therapy. but only in the hands of an expert. Dr. Ross Golden's technic which he permits me to quote is as follows: "Treatments, six in all, are given at intervals of two weeks, and have the following factors: 130 K.V., 50 cm. target skin distance, 3 mm. aluminum filter. 75 R are given at a sitting over each side of the neck. The field is small, measuring about 3 cm. by 9 cm. The upper margin of the field includes the lobe of the ear, and the long axis of the field comes downward and forward approximately parallel with the nasopharynx. The small field is used to avoid irradiation of the parotid gland. This small field is obtained by cutting a hole of the necessary size in a piece of thick lead foil."

In older children if the antrums are found to be involved they may well be irrigated at the time of the tonsil operation, especially for cultures for vaccine. Continual irrigation of the antrums should not be done, nor is it necessary, for as the infection is controlled the sinuses also usually clear.

In adults, both young and old, the foci of infection are found in teeth, tonsils and sinuses, rarely in the adenoid tissue. The teeth, especially in the upper jaw, are important as they may be primary factors in sinus infection. Apical and peridental infections should be cleared up and tonsils and adenoids should be removed if definitely infected.

NASAL SINUSES AND THEIR RELATION TO ASTHMA. Three important questions arise. Is the sinusitis an infection or a response to inhalant and food allergies as Hansel[20] believes? If an infection, is sinusitis a local allergic tissue reaction to the infection? Finally, is the sinusitis primary to and the cause of the asthmatic reaction? These questions have been fully considered in papers by myself and as co-author with Grove[4, 18, 19] and I shall summarize only briefly the evidence. In all of our cases sinusitis is of the hyperplastic type, that is, there is definite irreversible organic tissue change.

With regard to the first question one half of the patients with hyperplastic sinusitis do not have any demonstrable or clinical allergy to foods and inhalants. Carefully observed hay fever patients never show by transillumination or by roentgenograms of the sinus any evidence of membrane edema during acute allergic exacerbations due to pollen. The microscopic examination of tissues removed at operation from patients with hyperplastic sinusitis uniformly shows bacteria deep in the tissue beneath the basal membrane.

The belief that the tissue reaction is allergic is based upon (1) the presence of eosinophile cells in the hyperplastic membrane, (2) a tissue reaction in the antrum following autogenous vaccine injections (a local symptomatic reaction) together with (3) the evidence of a basic allergic constitution as determined in some patients by a lineage positive for allergy as well as (4) the presence of other allergies in about one third of the cases.

The final question deals with the sinusitis as primary to and therefore causative of the bronchial allergy. The evidence is based upon a study of cases of hyperplastic sinusitis. Their histories show that nasal symptoms and even nasal and sinus surgery preceded the symptoms of asthma by many years in a large percentage (over 50 per cent) of the cases. This is confirmed by clinical observation of our cases over a number of years. The presence of hyperplastic sinusitis has been recognized long before asthma developed. A further reason which supports this thesis is the resultant satisfactory improvement or disappearance of asthma following elimination of the primary sinus infection in about 80 per cent of the cases. The improvement is not immediate, but is progressive for a varying number of years after operation.

It seems likely then that hyerplastic sinusitis is a local allergic tissue response to infection and to infection alone, and that it is primary to and causative of the asthmatic condition which in its turn is also an allergic reaction.

In an evaluation of results of sinus surgery from the medical point of view, that is the effect on the physical condition of the patient as a whole including asthma, my observations from past experience lead me to condemn antral irrigations as a therapeutic procedure. Simple antrostomy as an operation of choice is not effective, for absorption from the infected membrane continues to produce the symptoms of the allergy. The so-called Caldwell-Luc operation is the procedure of choice. Resection of the septum is frequently performed but is not indicated except in the rare cases of mechanical blocking. From the medical angle it does little or nothing to relieve the absorption from infected sinuses.

There are, however, points to be considered carefully before recommending sinus surgery. (1) There must be definite evidence of sinus disease. (2) The cases must be carefully selected on the basis of physical condition and the reasonable probability of adequate recovery. Extensive organic change in the lung, as emphysema and fibrosis, or in the heart, as cor pulmonale, contraindicates operation. Rarely is an operation indicated before the age of twenty-five years. (3) The operation must be complete and superlatively well done. (4) There must be a prolonged period of convalescence. Epithelization of the antrum is not complete inside of six to eight weeks. (5) Adequate after-care must be insisted upon during convalescence, and allergies of the skin-reacting type, if present and involving the respiratory tract, must also be treated. (See Chapter 9.)

Prevention of Recurrences. The operations mentioned for the removal of foci do not of themselves remove all infection, but do eliminate much of the primary areas while leaving behind the secondary areas in the lungs, bronchi and in hilum glands. The most that an operation can do is to relieve part of the strain and give nature and the natural resources of the patient the best possible chance to recover. To this end one must seek to prevent recurrences of upper respiratory infection by avoiding contact with sources of infection and by stimulating the development of immunity against residual infection in bronchi and hilum glands by vaccine therapy as previously indicated as well as by attention to rest and general nutrition.

Other measures to prevent recurrences may be used. Sulfadiazine may be given in doses of 1.0—2.0 gm. a day (children 0.5—1.0 gm.) over several weeks or months. The avoidance of contact with acute or chronic respiratory infections which occur in school, at work and at home is really important. This is difficult, but when feasible older children may be sent away to school where the climate is mild. This often leads to very satisfactory results. Another important precautionary measure is the treatment of associated allergies of the skin-reacting type, especially those affecting the nasal and bronchial tracts.

General Management. EDUCATION OF THE PATIENT. The asthmatic patient requires careful management and must cooperate for best results. To get this assistance from him he must be educated as to his illness, the immediate causes as well as the nature of the underlying constitutional defect. When this latter is made clear then the reason for the long continued medical supervision, for it must be long, becomes likewise obvious. He is then aware that he still retains the basic condition for a return of asthma, perhaps from a new infection or from a new allergy. He understands, as the physician should, that absence of asthma is due to the avoidance of the cause and is not due to a cure of the allergic state. The possibility of a return is ever present. To get well the asthmatic patient must avoid fatigue, worry and any physical effort that produces dyspnea. Physicians would do much better by these patients if they themselves would appreciate and would make their patients understand that they should be handled much as tuberculous patients are, with long periods of convalescent care, especially in the early stages of treatment following operative measures.

NUTRITION. Nutrition is important for the patient's general welfare and is essential to the development of a protective immunity. There should be no unnecessary or foolish restrictions of important foods unless supported by sound clinical observation. Vitamin therapy of sensible proportions may be used if indicated and iron and liver therapy if the patient is anemic. If overweight, he should gradually reduce, but if underweight or emaciated, as is more frequent, a building-up program must be outlined and followed.

CLIMATE. Children with recurring infection certainly do better in regions where they may run and play outdoors, avoid sharp changes in weather and get a maximum of sunshine. But climate will not cure the patient with chronic asthma due to a focal infection. A balmy climate not too dry is very helpful to the patient convalescing from a sinus operation.

MISCELLANEOUS THERAPEUTIC MEASURES. Breathing exercises, physiotherapy of various types, short wave, ultraviolet and infra-red rays and baths are all useful therapeutic measures in their way but only in so far as they may contribute to the mental and physical improvement of the patient.

For no chronic disease have more so-called remedies been suggested than for asthma. It is hardly necessary to give a detailed discussion of each. Let it suffice to give a list of procedures or drugs that have been given critical trial, have failed, and should *not* be used: deep roentgen ray therapy to chest or spleen, ultraviolet irradiation of the blood, lipiodol, which of course must be used in diagnosis if patient is not iodine-sensitive, although it is not of therapeutic value, histamine, histaminase (Torantil), ascorbic acid and ethylene disulfonate. Hapamine has been evaluated, and results as yet have not been satisfactory. Sympathectomy has not yielded results that warrant its further use. The more extensive operation of bilateral resection of the posterior pulmonary plexus as reported by Rienhoff and Gay[21] is rarely applicable and cannot be recommended for general use, in view of the fact that indications for a probable satisfactory result are not clearly defined and the mortality is high. However, eight of twenty-one patients received striking benefit according to the latest reports by these authors.

Results. Perhaps more than in any other disease the results are directly proportional to the diagnostic and therapeutic skill of the physician and the cooperation he is able to secure from the patient. In the acute infective asthma of infancy and early childhood, with proper management and causal therapy, the results are excellent. The earlier the patients are seen and treated the more prompt and effective is the treatment. Infective asthma in later childhood and early adult life is often complicated by the coexistence of sensitizations of air-borne allergens and good results are more difficult to obtain. Both infective and non-infective factors must receive simultaneous attention as each contributes to the progress of the improvement in the other. Results are satisfactory when the treatment is adequate and the supervision prolonged.

In the older age group with asthma beginning after forty years of age, the results depend largely on the physical condition of the patient and the duration of the asthma at the time proper therapy is instituted. There is an exception to this worth remembering, and that is the patient who is thin with a sallow septic look even though his asthma may be of recent date. These are the patients who have suffered from the toxic effects of focal infection for years, but whose bronchial allergy is recent. In general the results in these patients are not good for there is no reserve of stamina on which to depend. The results of the treatment of asthma following sinus surgery are given in Chapter 9.

Prognosis. The outlook in infective asthma is good if cases can be seen and diagnosed early and proper measures promptly inaugurated. There is an idea that asthma in childhood will be outgrown but rarely is this true. Infective asthma in infancy may disappear occasionally without treatment, but only after considerable damage has been done. Frequently an allergy reappears in childhood as asthma from other causes than infection or as another allergy. In adults with chronic foci the earlier they are diagnosed and treated the better the prospect of a good result. *Early* diagnosis and treatment, combined with proper after-care, will do as much for the asthmatic patient as it has for the tuberculous. The profession and the laity need to be educated in this respect. Proper convalescent care and treatment definitely improve the prognosis.

Preventive Therapy. There is no doubt in my mind that infective asthma may be prevented to a definite extent. With the allergically predisposed children and infants the pediatricians have a wonderful opportunity. Everything done to prevent infectious disease—pertussis, measles and diphtheria—is an important step. Their efforts should be extended to a more effective control of contacts with parents and especially nurses having chronic sinus disease. I also advise the early removal of infected tonsils and adenoids. It is not now the usual custom to do this before the fifth or sixth year of age. A careful survey of my cases shows that this delay is not warranted in so far as the allergic child is concerned. The supposedly poor results of early operation are not apparent in my patients.

Further, in allergic families, the infants should be studied by the use of passive transfer tests to determine their allergic potentialities and the types of contacts that should be avoided before clinical symptoms appear. The child's entire physical future is contingent upon proper nutrition and avoidance of infection.

A recent annual report of the U. S. Public Health Service is highly significant. Checking back on the rejectees in one area it was found that over 96 per cent had defective teeth and 70 per cent were considered undernourished when examined at school fifteen years earlier. It is in the realm of preventive medicine that the great opportunity lies and no one has a better chance than the pediatrician who is interested in and understands allergy.

In adults there is no doubt but that the prevention or early removal of foci of chronic infection will break the chain of events that leads to asthma. Grove and I[4, 18, 19] have a small group of allergic patients in whom definite hyperplastic sinusitis has received operative attention before asthma had developed and in no case has asthma yet appeared. This is not proof, for the group is small, but it is suggestive. One of the cases in our group affords an illustration. Patient J. W. had ragweed hay fever for five years and was then treated and observed by Grove and myself from 1924 to 1934. During this time we had an opportunity to watch the development of a hyperplastic antritis. Steadily increasing winter recurrences of bronchitis led us to advise surgical intervention on the sinuses which was done in 1934 when the patient was fifty-two years old. To date, 1945, the patient is well with only an occasional mild winter cold, actually three in eleven years, and no asthma has yet developed.

The avoidance of respiratory infections, better diagnosis and more complete and earlier removal of infected foci are steps in the right direction toward the prevention of infective asthma.

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Pharmacopeia of Asthma

A List of the Drugs Commonly Used and Mentioned in the Chapters on Non-Infective and Infective Asthma

The dosages here stated are for adults and for children over twelve years of age. For infants and children under twelve years of age a conservative proportionate dose is represented by a fraction whose numerator is the patient's weight and whose denominator is 150. For example, an infant weighing 25 pounds would receive one sixth of the adult dose. Such rules are general and only approximately correct.

EPINEPHRINE; SUPRARENIN; ADRENALIN—(Chloride or Hydrochloride)—A Vasoconstrictor.

For Hypodermic Use:—(1) 1:1000 watery solution. Subcutaneous or intramuscular dose: 0.1–1.0 ml. (average dose 0.5 ml.) repeated as required. Use as little as possible, but sufficient to produce mild pallor and tremor. Massage injection site for two minutes for prompt effect. In severe shock from allergen extracts 0.5 ml. may be given intravenously, or 0.5–1.0 ml. may be injected directly into the heart.

(2) 2 mg. of powdered epinephrine crystals in 1 ml. of peanut oil. Subcutaneous or intramuscular dose: 0.4–1.0 ml. at 8 to 12 hour intervals. For slow absorption to maintain prolonged effect; usually available in purified peanut oil; may cause uncomfortable local reactions. A similar preparation in gelatin (Armour) may be used instead when again commercially available.

For Inhalation Use:—1:100 watery solution available in 5 ml. vials. Use only in special nebulizers and inhale deeply through mouth a few times. May be repeated as needed.

Use all epinephrine preparations with care, proportioned to the response of the patient, and in reduced dosage in hyperthyroidism, hypertension and serious cardiac disorders.

EPHEDRINE—(Hydrochloride or Sulfate)—A Vasoconstrictor.

For Oral Use. Dose: $\frac{3}{8}$–$\frac{3}{4}$ grain (0.024–0.048 gm.) repeated every 4 to 6 hours. Available in capsules or in 3 per cent solution (approximately $\frac{3}{8}$ grain per 12 minims) or in syrup according to the National Formulary (1 grain per fluid ounce). Also available in satisfactory proprietary combinations with phenobarbital and theophylline as Amesec (Lilly), Amodrine (Searle), and Tedral (Maltine). Use one, rarely two capsules, every 4–8 hours. Similar combinations in enteric coated capsules are available for prolonged effect.

Note. All ephedrine preparations, like epinephrine, must be used with care and preferably in reduced dosage in hyperthyroidism, hypertension and serious cardiac disorders.

AMINOPHYLLINE: Theophylline 75 per cent, Ethylenediamine 25 per cent. Vasodilator; cardiac stimulant and diuretic. The reason for its beneficial effect in asthma is not satisfactorily explained.

For Oral Use: Tablets $1\frac{1}{2}$ grains (0.1 gm.). Dose: 1–2 tablets in water repeated 3 to 4 times daily, preferably after eating.

For Hypodermic Use: Intramuscularly, ampoules of 2 cc., $7\frac{1}{2}$ grains (0.5 gm.). *Dose:* One ampoule every 8 hours as needed. Intravenously, ampoules of 10 cc., $3\frac{3}{4}$ grains (0.24 gm.). *Dose:* One ampoule, rarely two, given slowly, may be repeated 3 to 4 times daily. May be given in the same syringe with sodium iodide.

For Rectal Use: Suppositories of 5 grains (0.324 gm.) are available. Cocoa butter (oil of theobroma) is the usual base. Glycerinated gelatin may be substituted. Dose: 2–4 suppositories daily as needed, or 4–6 tablets (readily soluble) in warm water as retention enema.

AMINET (BISCHOFF) SUPPOSITORIES: Adult size contains aminophylline 7½ grains (0.5 gm.) and phenobarbital sodium 1½ grains (0.1 gm.). Infant size contains aminophylline 4 grains (0.25 gm.).
For Rectal Use: Dose: A suppository may be used at 4–6 hour intervals.

THEOPHYLLINE.
For Oral Use: Dose same as that of aminophylline.

SEDATIVES.

1. Opium Derivatives:
   - (a) Morphine Sulfate: *For oral or hypodermic use:* Dose: ⅛–¼ grain (0.008–0.015 gm.) as indicated.
   - (b) Codeine Sulfate: *For oral use:* Dose: ⅛–1 grain (0.008–0.06 gm.) as indicated. *For rectal use:* Suppositories ½–1.0 grain (0.03–0.06 gm.).
     Codeine Phosphate: *For hypodermic use:* Dose: ¼–1.0 grain (0.015–0.06 gm.) as indicated.
     Codeine: *For oral use:* Elixir Terpin Hydrate and Codeine. ⅛ grain (0.008 gm.) per dram. Dose: One dram (4.0 ml.) and repeated as needed.
   - (c) Pantopon (Roche): Causes less nausea, excitation and respiratory depression than morphine.
     For hypodermic use: 1 cc. ampoules, ⅓ grain (0.02 gm.). Dose: ½–1 cc. and repeated every 4 to 6 hours as indicated. 1 grain equals ½ grain morphine.
   - (d) Dilaudid Hydrochloride: Dihydromorphinone.
     For oral use: Tablets 1/48–1/24 grain (0.0013–0.0025 gm.) may be tried if other morphine preparations are not well tolerated.
     For hypodermic use: 1/32 grain (0.002 gm.).
   - (e) Dionin (Merck): Ethyl morphine hydrochloride.
     For Oral Use: ¼–½ grain (0.015–0.03 gm.).
2. Barbiturates: Sedative and mildly analgesic. Among the more commonly used are:
   Allonal (Roche): Tablets 4½ grains (0.29 gm.). Dose: 1–2 tablets at bedtime.
   Amytal (Lilly): Tablets ¼ grain (0.015 gm.), ¾ grain (0.05 gm.), 1½ grains (0.1 gm.). Dose: 1–2 tablets at bedtime. Maximum sedative dose 3 grains (0.19 gm.).
   Sodium Amytal: Ampoules 0.25 gm. for hypodermic use.
   Dial (Ciba): Tablets ½–1½ grains (0.03–0.1 gm.). Dose: ½–1½ grains at bedtime.
   Nembutal (Abbott): Capsules 1½ grains (0.1 gm.) as hypnotic. Dose: 1 or 2 capsules at bedtime, or 1 repeated in 2–4 hours if needed.
   Phenobarbital (Luminal—Winthrop): Tablets ¼–1 grain (0.015–0.06 gm.). Dose: As a sedative ¼–½ grain 3 times a day. As hypnotic: Phenobarbital sodium 2–3 grains (0.12–0.2 gm.) freshly prepared in 20 per cent solution in distilled water for hypodermic use at bedtime.
   Seconal (Lilly): Tablets 1½ grains (0.1 gm.). Dose: One tablet at bedtime, and repeated in 2–4 hours if necessary.
3. Sedatives: Miscellaneous.
   Demerol Hydrochloride: *For oral use:* Tablets 50 mg. Dose: 1–2 tablets. *For hypodermic use:* Ampoules 2 ml. (100 mg.). Intramuscular dose: 100 mg.
   Sodium Bromide: *For oral use:* Dose: 5–15 grains (0.3–1.0 gm.). Repeat every 4 to 8 hours as needed. Effervescent tablets 15 grains (1.0 gm.) (Burroughs-Wellcome) are very acceptable.
   For rectal use: Dose 30 grains (2 gm.) alone or combined with chloral hydrate 15 grains (1.0 gm.) in water for retention enema.
   Chloral Hydrate: *For rectal use:* Dose: 5–15 grains (0.3–1.0 gm.). Not a seda-

tive of choice, but excellent in combination with bromide as a retention enema.

Paraldehyde: Hypnotic, antispasmodic. *For oral use:* Dose: 1–2 drams (4–8 ml.) in orange juice at bedtime. *For rectal use:* Dose: Is well tolerated in doses of 2–4 drams in a retention enema with water.

Ether in Oil: *For rectal use:* Equal parts of ether in any bland oil, especially olive oil (avoid cottonseed oil in asthmatic patients). Dose: 4–6 ounces for adults (120–180 ml.), given slowly. It is not as useful as paraldehyde and not highly recommended for children.

EXPECTORANTS.

Potassium Iodide: *For oral use:* Dose: 5–15 grains (0.3–1.0 gm.) in water. Preferably after eating, 3 or 4 times a day. This drug is occasionally surprisingly effective in asthma, especially when the secretion is scant. Alone or in one of many combinations it is an old reliable and should always be given a trial. It occasionally gives an edema reaction in allergic patients. A trial by mouth should always precede the use of iodine as lipiodol for bronchograms.

Sodium Iodide: *For intravenous use:* Available in 10 ml. ampoules 15 grains (1.0 gm.). Dose: 15 grains once or twice a day. *An oral dose* should always precede the intravenous injection in allergic patients. It may be given with aminophylline.

Hydriodic Acid: Syrup. Dose: 1 dram (4.0 ml.) repeated 3 to 4 times a day. Is especially useful in children.

Ipecac: Syrup. Dose: As an expectorant 15 minims (1 ml.). As an emetic ½ ounce (15 ml.).

Ammonium Chloride: Dose: 5 grains (0.3 gm.) is useful in many of the standard expectorant prescriptions (Stokes's) or combined with Brown mixture. Is also used in enteric coated capsules to promote the diuretic effect of mercupurin.

CARDIAC STIMULANTS.

Digitalis: The dried powdered leaf standardized (1 cat unit = 1½ grains or 0.1 gm.), is the basis of all therapy of cardiac dysfunction. It is used in asthma solely for that complication.

Strophanthin (Lilly): More rapid and more effective in emergency conditions of the heart than digitalis. *For hypodermic use:* In tablets 1/100 grain (0.65 mg.). Dose: ½–1 tablet by intramuscular or intravenous injection.

Coramine (Ciba): A cardio-respiratory stimulant. *For hypodermic use:* in ampoules (1.5–5.0 ml.). Dose: 1–3 ml. subcutaneously or intravenously.

Caffeine Sodiobenzoate (Caffeine 48 per cent). A cardio-respiratory stimulant. *For hypodermic use:* Dose: 3–5 grains (0.2–0.3 gm.).

MISCELLANEOUS.

Acetylsalicylic Acid (Aspirin): Dose: 5–15 grains (0.3–1 gm.). Is curiously effective in an occasional asthmatic patient. *Warning:* It should never be given in the usual dose without careful questioning. If a patient has never used the drug a trial dose of 1/10 grain (0.006 gm.) is first indicated. Allergy to aspirin is common and fatalities have occurred.

Mercupurin (Campbell Products): Diuretic. *For hypodermic use:* ampoules 1.1–2.2 ml. Dose: 1–2 ml. intravenously. More effective when preceded for 2 to 3 days by Ammonium chloride (enteric) 90–150 grains (6–10 gm.) by mouth.

Nuporal (Ciba): A cough lozenge. Each contains 1/65 grain (0.001 gm.) nupercaine. Dose: Dissolve one lozenge slowly in the mouth every 2 to 3 hours. Children: ½–1 lozenge every 3 hours.

Asthma Powder: Stramonium combined with nitrites. For inhalation only. Cigarettes are also available.

8. The Differential Diagnosis of Bronchial Asthma

HORACE S. BALDWIN

In considering the differential diagnosis of bronchial asthma it is well to remember that fundamentally it is a form of paroxysmal dyspnea, the characteristic features of which are prolonged expiration and wheezing. There are three classes of patients as seen in clinical medicine who must be considered in any topic of this sort. First, the true or typical bronchial asthmatic. Second, the true asthmatic with structural changes in the heart, lungs or other organs which may obscure the true picture, and third, the group of patients who do not have bronchial asthma but have certain other conditions which may simulate the symptoms and physical signs of true asthma.

True bronchial asthma is a reversible reaction characterized usually by cough, wheezing and expiratory dyspnea, usually associated with a family history of allergy, often related to definite inhalant or food sensitivities as determined by skin tests, or associated with nasal sinus infection with or without polyps. The physical signs in the chest consist practically always of wheezing, sibilant and sonorous râles and rhonchi, especially in expiration. When the asthmatic attack is over the physical signs disappear. The sputum usually contains eosinophile cells.

Asthma Associated with Structural Changes. When true bronchial asthma is accompanied by structural changes, these may obscure the picture, thus interfering with proper handling of the essential asthmatic nature of the trouble. A number of brief case abstracts will be given which indicate the importance of properly interpreting the asthmatic component in patients with asthma and structural disease.

A patient may have *coronary artery disease* and asthma, but this does not necessarily mean that the asthma is cardiac in origin:

A man, aged fifty-three, a plaster moulder in a gumdrop factory, was admitted to the hospital with asthma of fifteen months' duration. An attack of coronary thrombosis necessitated absence from work for three months and during that time the patient had no asthma. Return to work led to asthma again. Skin tests showed: Acacia ++++, Timothy 100 +, Ragweed 100 +. Roentgenograms of the sinuses were normal. Examination of the ears, nose and throat was negative. The patient's work was arranged to avoid contact with factory dust and timothy and ragweed inoculations were given. Since then he has had very little asthma.

Asthma may start relatively late in life and be associated with *changes in the electrocardiogram*. That this finding may have no relation to the asthmatic attack is illustrated in the following case:

A man, aged fifty-four, had asthma which started on his fiftieth birthday, August 24. From then on his asthma occurred yearly at this time. Skin tests showed reactivity to the pollens of ragweed and grasses. Electrocardiogram showed left axis deviation. The QRS induction time was at the upper limits of normal. The heart rate was rapid. The splitting of the QRS complexes indicated myocardial disease. He was given immunizing injections of ragweed, the grasses and dust. When last heard from seven years later, he reported having had no more asthma and his general health was excellent.

Not all asthma associated with *bronchiectasis* is secondary to an organic disease of the lung. This holds true also for lung abscess and tuberculosis. The following case is cited to show an instance of asthma and bronchiectasis in which the asthmatic component was largely separate and distinct from the bronchiectasis:

A man, aged sixty-two, thirty-five years previously, while working in a button grinding factory, developed a chronic cough. He had since worked as a plasterer. He had a history of perennial asthma which was worse in the Fall. September 10, 1942, he was admitted to New York Hospital with a pneumothorax of the left lung, and signs of asthma, emphysema and chronic bronchiectasis. He was sensitive to ragweed and house dust for which he was immunized. Since then his asthma and cough have lessened but excessive expectoration persists.

Even with *obstruction in the upper respiratory tract*, causing dyspnea both in inspiration and expiration, it is important to study the asthma from the standpoint of sensitivities and sinus infection. The following case is important from these angles:

A woman, aged forty-nine, had asthma starting in June 1933. She had a past history of hay fever every August since 1919. Skin tests showed her to be sensitive to ragweed and dust. Roentgenograms of the sinuses showed a cloudiness of the right ethmoidal cells and the antrum. The physical examination showed the usual signs of asthma, but the right lobe of the thyroid had a large calcification which displaced the trachea to the left and caused stridor. The basal metabolism was normal. Roentgenograms of the trachea following lipiodol injection showed a calcified mass on the right with the trachea displaced to the left. The right lobe of the thyroid was removed, the stridor disappeared and the asthma improved remarkably. Since then the patient has improved with injections of ragweed and dust, and an occasional treatment for the sinuses.

It is sometimes difficult to distinguish *hysteria and malingering* in the asthmatic patient. At the same time it is important not to attribute to psychosomatic disturbances asthmatic symptoms which are based on sensitivities and infection. My own classical example of this is a neurotic girl of fifteen who had had asthma every September. The psychiatrist called in to see her said that her asthma recurred at this time of the year because of an inferiority complex connected with her poor work at school, which recommenced annually at this time. Suffice it to say that with the usual allergic technic sensitivity to ragweed was demonstrated, and since then, with injections of ragweed extract, she no longer has trouble when school starts in September.

At times hysteria and malingering may occur in the true asthmatic.

Here the problem must be handled with considerable intelligence. The following case illustrates this:

A boy, aged sixteen, had asthma of several years' duration. He was sensitive to the pollens of grasses and ragweed, animal epidermis and house dust. He had ethmoiditis and marked deviation of the septum. There was a psychoneurotic family history. While in the hospital under observation, he complained of an asthmatic attack. He was observed to force his respirations, throw himself about in bed with extreme hyperextension. He was discharged to a boys' school which had an extremely intelligent headmaster. The patient was given specific immunization and his septal deviation was corrected. His asthma greatly improved.

Turning to the other side of the picture, structural changes in the asthmatic may represent the most important feature of the condition. In these cases it is necessary to evaluate the various factors with the utmost care, realizing in some the futility of allergic methods in dealing with the problem.

The following case is one in which *chronic cardiac valvular* disease and resultant failure were paramount:

A woman, aged thirty-two, had severe chronic asthma. The skin tests were negative. She had chronic hyperplastic sinusitis, asthma and chronic rheumatic cardiac valvular disease. All the usual methods to control asthma, including sinus surgery, had no effect. The factor of cardiac failure seemed most important in dyspnea leading to asthmatic breathing.

The following case illustrates the importance of *chronic pulmonary emphysema*, especially when associated with coronary sclerosis:

A man, aged sixty, had suffered from asthma since childhood. His thorax was thick, and showed emphysema with many musical râles. His blood pressure was 180/110. There were wide areas of hyperresonance over the chest, liver and heart. His breath sounds were diminished, and there was a wide substernal angle. Hoover's sign was present. The skin tests were negative. Sinuses showed thickened membrane with polypoid tips of turbinates. Electrocardiogram showed left ventricular preponderance with evidence of coronary sclerosis.

Hypertension and *coronary disease*, especially when accompanied by uremia, may give rise to asthmatic breathing, particularly when occurring in patients who have at any time in their lives had asthmatic manifestations. Uremic and diabetic acidosis may produce expiratory dyspnea connected with the attempt to maintain a normal blood *p*H, and this emphasis on the expiratory phase of respiration may lead to an asthmatic type of breathing, especially in the patient who has had asthma at some other time in his history. The following case illustrates the combination of hypertension, coronary artery disease and uremia leading to asthmatic breathing:

A man, aged forty-nine, complained of substernal pressure for eleven months and mild asthma consisting of wheezy breathing on exertion. He had had mild asthma twenty years before which had not recurred until the present illness. The physical examination showed breath sounds diminished with harsh accentuated quality to the expiratory phase. Wheezes were elicited on exertion. His heart was enlarged and his blood pressure was 208/84. The urine showed a heavy trace of albumin with casts. The blood urea nitrogen was 80 mg. rising to 113 mg. 5 per cent phenolsulfonephthalein was excreted in two hours. In the electrocardiogram, the form of the T waves and R-T segments as well as splitting of the QRS complexes indicated coronary artery disease. Roentgenograms of the chest showed the heart to be enlarged. All the skin tests were negative.

Conditions Simulating Asthma. The last group of cases to be described comprises those conditions which are not truly bronchial asthma but may simulate its symptoms and physical signs. The first of these, comprising those cases with obstruction in the upper respiratory tract which may lead to dyspnea both in inspiration and expiration, may, in some cases, be confused with true bronchial asthma. Edema of the larynx, diphtheritic swelling of the larynx, foreign body in the larynx, laryngeal papillomata or fibromata, stenosis of a bronchus may lead to the diagnosis of asthma, but rarely, because the dyspnea is so strikingly inspiratory as well as expiratory in the vast majority of the cases.

When the obstruction is lower down in the bronchial tree, as with foreign bodies, there may be a real diagnostic problem to distinguish the truth of the matter, as Dr. Chevalier Jackson, Jr., and others have so well pointed out.

Two cases are reported to illustrate the asthmatic type of breathing which may accompany the presence of *foreign bodies* in the bronchial tree.

A child, aged twenty-two months, ten days before admission choked while eating nut cake and immediately coughed. Ever since then her breathing had been rapid with a whistling sound in expiration. Physical examination showed hyperresonancy throughout both lungs. Breath sounds were diminished over the whole right lung; expiration was prolonged with wheezing similar to that found in asthma. The left lung seemed normal. Bronchoscopy revealed no foreign body. Roentgenograms of the chest showed the upper left lobe radiating poorly. The child gradually improved and at the present writing has had no more symptoms.

A man, aged sixty-two, visited his dentist two days before the onset of his present illness, about three weeks previously. While his dentist was prying at a gold capped tooth, the cap fell back and was apparently swallowed. Then followed spasmodic coughing, pain in the left anterior chest, fever, drenching sweats and wheezy respirations. Roentgenograms of the chest showed, in the left hilar area, a shadow of infiltrated density with the shape of a dental crown. The patient left the hospital to see Dr. Chevalier Jackson. Shortly after his arrival in Philadelphia he coughed up the crown. His recovery was complete.

Obstruction from without the bronchial tree may be due to an enlarged *thyroid* or *thymus*, to a *thoracic aneurysm* or to *tumors*. A case of bronchial asthma greatly aggravated by pressure from an enlarged thyroid has already been described (p. 163). Neoplasms of the lung, whether primary or metastatic, may cause pressure and resultant wheezing and asthmatic breathing, the cause of which may be difficult to determine unless the possibility is kept in mind. The following case is reported in which a bronchogenic carcinoma gave as its first symptom an attack of asthmatic breathing:

A man, aged sixty-nine, had his first attack of asthmatic breathing several weeks before admission to hospital. The diagnosis was originally bronchopneumonia with asthma. A roentgenogram of the chest showed partial collapse of the right upper lobe with shift of mediastinum to left and parenchymal infiltration from hilum. Bronchoscopy showed bronchial carcinoma.

In concluding an enumeration of conditions which may lead to asthmatic symptoms it is necessary to mention *periarteritis nodosa.* This condition, through involvement of the pulmonary vessels, may sometimes give rise to asthmatic breathing. Here, the blood picture in which heavy eosinophilia is occasionally a striking feature, the varied clinical manifestations of the disease due to the preponderant involvement of the visceral arteries, and finally the typical pathologic changes sometimes found in biopsy, may give the final clue to the real diagnosis.

It is important before closing this subject to reiterate that asthmatic breathing is a symptom and not a disease. Why some cardiac and some uremic patients, not to mention those with other conditions, have asthmatic breathing and others do not is difficult to understand. It would seem that the best explanation would lie in the neurophysiology or chemistry of the respiratory tract. In other words, some patients who may be potential asthmatics have a typical pattern of respiratory response when the respiratory mechanism is under stress and strain and asthmatic breathing results when the dyspnea is pronounced. Swineford has elaborated this theory more at length in one of his articles on the subject.

While in most cases the diagnosis of bronchial asthma is clear-cut, it is worthwhile studying each case thoroughly, not only as a problem in allergy and respiratory infection, but from the larger aspects of internal medicine as well. In addition to skin testing, roentgenograms of the sinuses and special nose and throat surveys, it is important to x-ray the chest, examine the blood serologically, do a complete blood count and urinalysis. Special technics such as the electrocardiogram, bronchoscopy, blood chemistry, sputum examination for eosinophile cells, may be necessary if indicated. In these ways much information of help to the true asthmatic, as well as in those cases complicated by structural changes, may be obtained. Finally, in that group in which the asthma is simulated, delay in the proper approach to the real problem will be avoided.

9. *Hyperplastic Sinusitis and Asthma*

R. CLARK GROVE

Introduction

THE importance of disease of the sinuses in the diagnosis and treatment of asthma is too little appreciated by many clinicians in the field of allergy. Some overlook the condition entirely and others take the position that it is merely part of the general allergic manifestation such as asthma and that it is not a cause. The studies that have been made in the Allergy Division of the Roosevelt Hospital on upper respiratory infections, which include sinusitis, have given us a point of view to clarify a few misconceptions and to prove that excellent results can be produced by careful intelligent handling of disease of the paranasal sinuses.

It is necessary in the first place to establish the fact that there is a definite pathologic condition in the sinuses, and in the second place to decide if this condition is an etiologic factor in the production of the allergic symptoms. It is true that quite often these patients are operated upon without sufficient pathologic change being present in the sinuses, and therefore no relief is produced. Many patients are also operated upon in whom sinus disease when present is not influencing their allergic symptoms, and likewise the result is bad. For instance, a patient whose asthma is due to pollens, house dust, or animal danders, or a patient whose urticaria is due to the ingestion of certain foods or to a contact exposure, will not be helped by operation on the sinuses. On the other hand, if the patient's asthma or urticaria is precipitated at certain times, or is made worse, by upper respiratory infections involving the sinuses, then such an operation will be of value.

Thus, to discuss the topic in hand intelligently, it is necessary to remember these previously mentioned facts: namely, that certain allergic manifestations are of the skin-sensitive type, while others are of the non-sensitive or infective type (see p. 25). The first group is diagnosed by positive skin tests, whether by the intradermal or scratch method, the patch test and the use of elimination diets. The second group is usually negative on skin testing and the presence of disease in the upper respiratory tract as well as the influence of such infection on the allergic symptoms can be demonstrated. In addition to the skin-sensitive and the infective types there is the combined type, that is, the patient may show skin reactions and also the presence and influence of foci of infection. If these three groups are kept in mind, one is in a better position to evaluate the importance of otolaryngologic pathology in the treatment of allergic disease.

The close relationship of the sinuses to the lungs has been shown by Mullin.[1] He injected the maxillary sinuses of rabbits with a suspension of India ink and traced it to the submaxillary and internal jugular nodes, the lymphatic ducts, the superior vena cava and the right side of the heart and thence to the lungs. Infection may travel by this route to the lungs, but it is more frequent to find the lungs infected by postnasal dripping of mucopus which infects the tracheal and bronchial mucosae. However, the membranes of the smaller bronchi and bronchioles may also be reacting allergically to the bacterial products or their toxins.

According to Adam,[2] Herck of Freiberg in 1844 first recognized the importance of sinus disease as a cause of asthma. However, it was not until 1871 that Voltolini[3] showed the effect of sinus surgery on asthma when he reported a case of asthma in which a cure followed polypectomy. Since that time the frequency and importance of sinusitis in asthma have been argued pro and con and its treatment has varied from conservative to radical surgery, although many physicians still advocate no surgery at all.

Incidence

The reports in the literature on the frequency of sinus disease in asthma patients show a wide variation. This is due in large part to the method of diagnosis, that is, whether it is based on rhinoscopy alone or on roentgenograms. Gottlieb[4] found sinusitis present in only 26 per cent of 117 patients with asthma. Dundas-Grant[5] stated that 63 per cent of 107 cases of asthma had sinusitis. Chobot,[6] in a group of eighty-four children up to fifteen years of age, found x-ray evidence of sinus disease in 67 per cent of the patients. Kern and Schenck,[7] after a careful study of 400 cases of asthma, found that 70 per cent had clinical sinusitis and 87.5 per cent showed x-ray evidence of disease. More recently, Kelley[8] reported that 89 per cent of 100 cases of asthma had rhinologic and x-ray evidence of sinusitis.

In a comprehensive study based on 688 cases of asthma, Cooke[9] found sinus disease to be the cause in 39 per cent of 257 cases with asthma beginning between ten and thirty years of age; 65 per cent of 171 cases between thirty and fifty years; and in 83 per cent of forty-two cases after fifty years. In the 688 cases, infection was the sole cause of asthma in 34 per cent and combined with sensitizations, such as danders, pollens or foods, it was an additional cause in 15 per cent, making a total of 49 per cent of all asthma caused by infections of all types, which include sinus, dental, tonsillar, pharyngeal and primary pulmonary infections. He excluded cases in the first decade since the tonsils and lymphoid tissues of the pharynx and nasopharynx are more important at that time, and found that 53 per cent of the remaining 470 cases were caused by infection, with 8 per cent being due to primary pulmonary infections, leaving 45 per cent with sinusitis as the only cause.

It is interesting to note that Bullen[10] in 1933 reviewed 93,000 admissions to three general hospitals in Rochester, New York, and found that 1.2 per cent warranted a diagnosis of disease of the paranasal sinuses. It was most frequent in the latter half of the first decade of life and between the ages of thirty and fifty or fifty-five years. He studied 400 of these cases of sinusitis and found that about one-fourth had some form of chronic non-tuberculous pulmonary disease, 12.25 per cent of them had asthma, while in 8.75 per cent their asthma actually began at the same time as the sinusitis or later. Bullen was not impressed with sinusitis as a cause of asthma, but when one considers that the percentage of allergic disease in the population is not more than 10 to 15 per cent, it is evident why this percentage of asthma, which is but one of the evidences of allergy, is so low, because hyperplastic sinusitis as a cause of asthma must occur in a person with an allergic constitutional background. Cooke,[9] in the previously quoted group of 688 cases, found that there was a positive antecedent history of allergy in 45 per cent of the entire infective group, and 52 per cent of the skin-sensitive group. Sixty-six per cent of 195 cases of asthma gave an antecedent history of asthma and there were other allergic manifestations in 34 per cent. Clarke, Donnally, and Coca[11] quoted 80 per cent with a positive antecedent history. Kern and Schenck,[12] after a survey of 345 cases of nasal polyposis, came to the conclusion that an allergic history or other allergic manifestations are always present.

Pathology and Bacteriology of the Nasal and Sinus Membranes

In my experience almost 100 per cent of the pathologic manifestations of sinusitis are of the hyperplastic or thickened membrane type as contrasted with the suppurative type. There may be exacerbations of infection when pus appears in the washings and neutrophils predominate in the membranes, but this is only temporary. A true hyperplastic membrane is much thickened, often infolding and polypoid, with desquamation of the cilia, a much thickened hyalinized basement membrane and in the tunica propria marked edema, glandular hyperplasia, proliferation of the connective tissue and eosinophilic, round and plasma cell infiltration (Fig. 9). In the chronic cases, neutrophils are not frequent. The bronchial and conjunctival mucosae have shown the same general characteristics on pathologic examinations. Polyposis occurred in from 30 to 35 per cent of my cases, which included many who had had previous operations. Kelley,[8] in his study of 100 cases of asthma, reported 26 per cent with polyps.

These membranes have been cultured (Grove and Cooke[13]), and it was found that 80 per cent were positive for one or more organisms. Only one of twenty-nine antral membranes was sterile, while sixteen of fifty-one ethmoidal and sphenoidal membranes were sterile. This is easily explained by the fact that most of these latter specimens were mucous or cystic polyps, the contents of which are usually sterile, the infection being in the cyst wall or underlying membranes. Thirty-four of the positive cultures yielded a single organism, which seems important from the standpoint of the value of the organism as an etiologic agent in the disease. A comparison of the organisms obtained from eighty-seven membranes with those grown from previous washings of the antrums showed that 43.7 per cent were different from any recovered preoperatively. I do not believe that the simple irrigation of an antrum with a clear return flow which yields a negative culture necessarily indicates a normal or non-infective sinus. Stained sections of the tissues removed from the sinuses demonstrated bacteria very definitely in 85 per cent, while the remaining 15 per cent were too questionable to be considered positive.

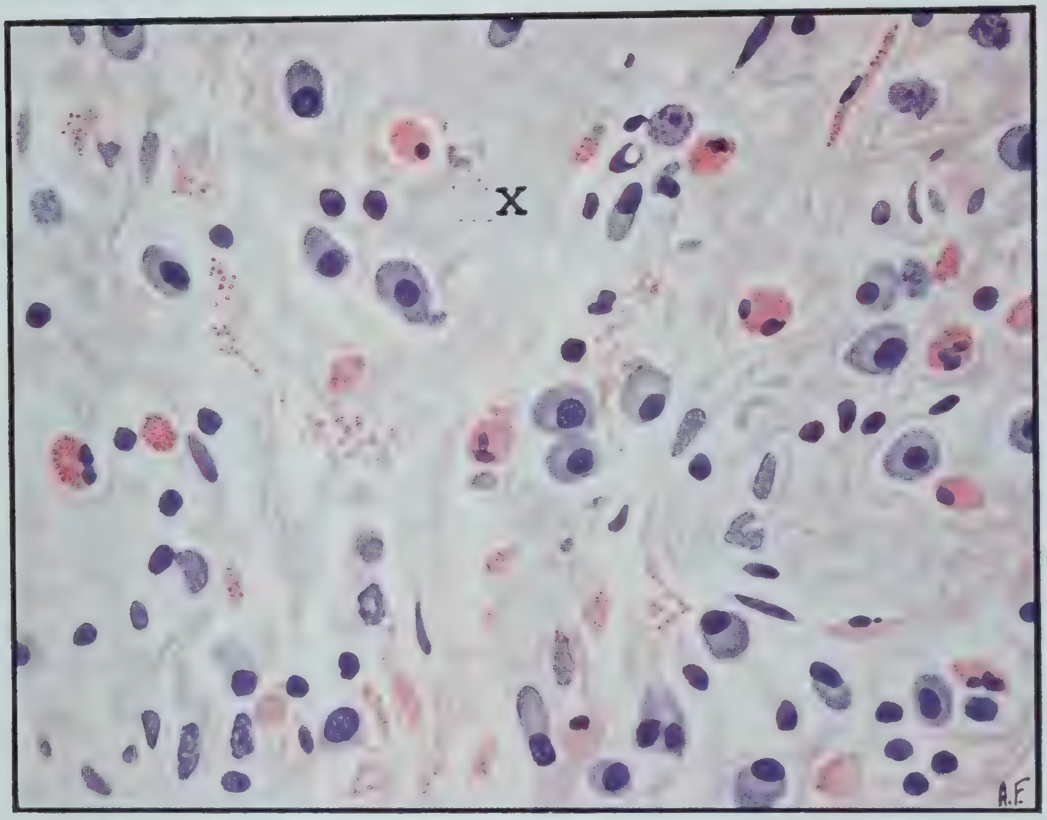


Fig. 9.—Hyperplastic antrum membrane. Note the extreme edema and abundant eosinophile cells and the clump of stained bacteria (X) deep in the tissues. (Magnified 1000 times.)

The percentages of bacteria obtained from a study of 108 antral membrane cultures made by Grove and Farrior[14] were as follows: staphylococcus, 57 per cent; Streptococcus viridans, 43 per cent; pneumococcus, 39 per cent; hemolytic streptococcus, 25 per cent; indifferent streptococcus, 3.7 per cent; Neisseria catarrhalis, 3.7 per cent; Proteus vulgaris, 0.9 per cent; Escherichia coli, 0.9 per cent; diphtheroid bacillus, 0.9 per cent; negative, 4 per cent. Kistner[15] in 1931 studied 400 sinus membranes culturally and found streptococci present in 94.5 per cent of the cases. Rosenow of the Mayo Clinic checked some of these specimens microscopically and agreed that the membranes were infected. Hansel,[16] Piness and Miller,[17] Ashley and Frick,[18] and Balmer[19] believed that organisms in the membranes are secondary invaders. This is not the opinion of Goodale[20] or of Kistner,[15] and is contrary to the opinion of Grove and Cooke.[13, 14, 28]

Diagnosis

The question now arises as to the diagnosis of hyperplastic sinusitis in allergic patients. This is accomplished by careful clinical, laboratory and x-ray examinations. The history of frequent colds, stuffiness, nasal discharge anteriorly or posteriorly, sneezing and headaches is important, but frequently all of these symptoms are absent. The nasal examination should include anterior rhinoscopy followed by the use of the nasopharyngoscope. The nasopharyngoscope is very important, as otherwise discharge from the antrum, posterior ethmoids and sphenoids, and small polyps posteriorly may be overlooked. Transillumination should be done, but if this reveals nothing abnormal, the examination is not complete. Good roentgenograms are very important, especially for diagnosing polyps and cysts of the antrum (Fig. 10).

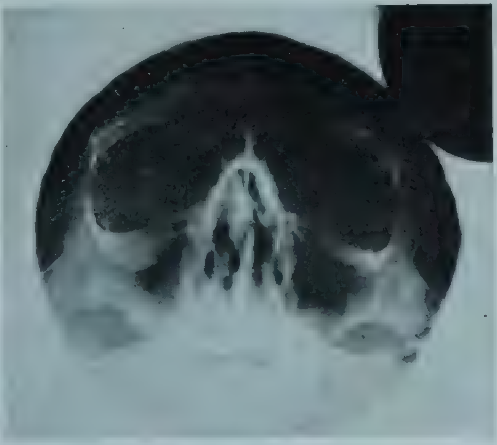


Fig. 10.—Plain roentgenograms showing extensive polypoid degeneration of the mucous membranes of the antrums.

In recent years, I have been making more use of radiopaque solutions in the diagnosis of sinusitis. The plain films may show only slight pathologic changes in the sinuses, especially the antrum, which often may not seem sufficient to justify an operation. In the infective type of allergic manifestations where it is necessary to eliminate all infection, I have resorted to the injection of radiopaque solutions such as lipiodol into the sinuses. It seemed to me that in these cases the iodized oil was too opaque and often obscured polyps or cysts if they were in such a position as to cause little defect in the marginal outlines of the sinuses. It was not until 1938 that Grove and Cooke[21] first applied thorium dioxide in these cases. We had a patient who was sensitive to iodine, so we decided to try a 25 per cent colloidal solution of this radiopaque chemical (Umbrathor). We were impressed with the delicacy, if one may call it such, of the shadows on the x-ray films. The solution, when diluted once or twice, seemed to produce a less dense shadow and the margins and backgrounds of the sinus were more clearly delineated. Since that time, I have injected over

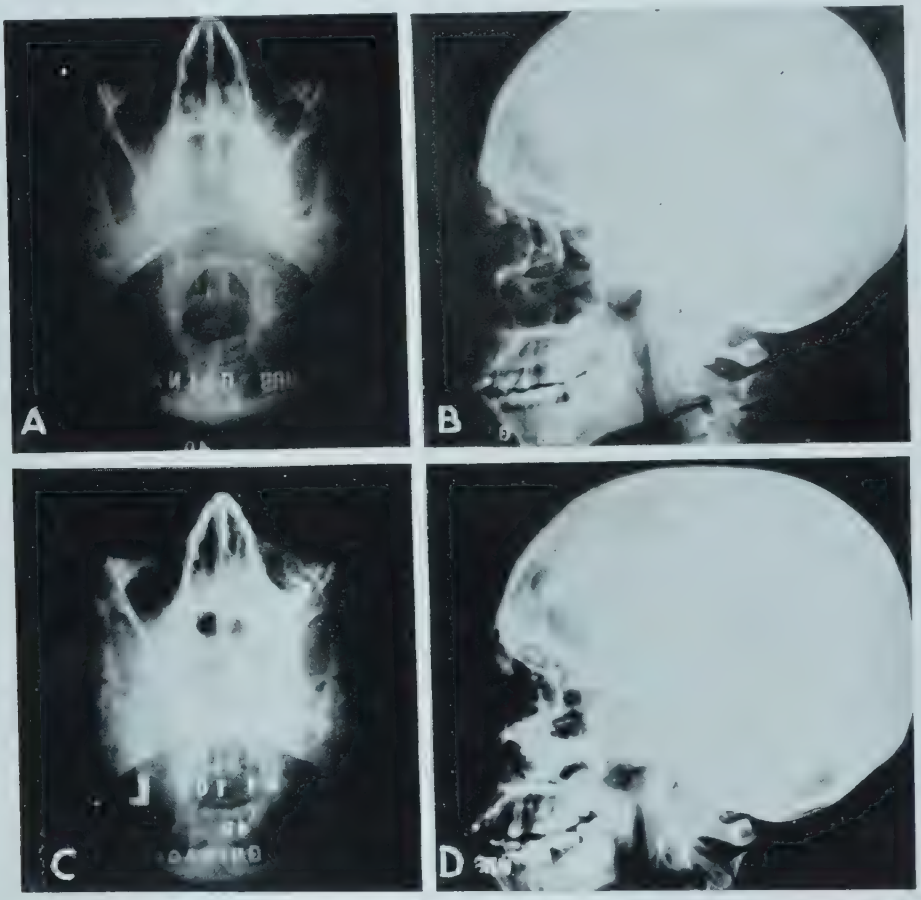


Fig. 11.—*A* and *B* are plain roentgenograms showing normal-looking antrums. The right antrum was hazy on transillumination. *C* and *D* are roentgenograms made after the injection of Umbrathor in the right antrum. Note the large filling defect due to the presence of polypoid changes in the mucous membrane. This polypoid disease was verified at operation.

200 sinuses without any untoward reactions. Figure 11 shows the advantages of the thorium dioxide solution over the plain film.

If the x-rays show evidence of the sinusitis, a lavage of the antrum or sphenoid sinuses is usually done. The return flow is centrifuged and examined microscopically for evidence of pus cells and eosinophils, and usually cultures are made for possible use as vaccines.

Treatment

Once the diagnosis of sinusitis is made, the proper form of treatment must be decided upon. If polyps are present in the ethmoids or sphenoids, they should be removed if the asthmatic condition justifies such a procedure. By removal of the polyps, I do not mean a simple polypectomy, but an exenteration of the ethmoids or sphenoids. Polyps, cysts and extensive thickening of the membrane of the antrums require a Caldwell-Luc operation. Satisfactory results have not been obtained by simple antrotomies or "window" resections. In conjunction with these operations, submucous resections and trimming the turbinates are done, if indicated, to improve sinus drainage and not for any direct benefit to the asthmatic condition. If the sinus infection is of a low grade or mild form, irrigations of the antrum, or if pus continues to be present and upper respiratory infections are frequent, occasionally antrotomy, removal of adenoids and tonsils and infected teeth and the use of vaccines, both autogenous and polyvalent, will suffice for treatment.

Regardless of the degree of sinusitis, complete allergic testing and treatment are necessary. A large number of patients with recurring polyps can be cured if the dust or other inhalant allergies are treated before and after the operation. Blood examinations including Wassermann, kidney and chest examination including roentgenograms, and sputum examination for tubercle bacilli, eosinophils, molds and spirochetes are usually indicated. Determination of increased sedimentation rate is often important in studying these infective cases. Recently the question of vitamin deficiency has been emphasized, and in certain cases vitamin assay is necessary.

Results

Table 21 shows the frequency of the various sinuses involved in asthma and the operations performed. The antrum is the most frequently involved and the ethmoids second. The frontal sinus is the least often involved. The most frequent operation is the exenteration of the ethmoids, with the Caldwell-Luc operation of the antrum being next in order.The external operation on the frontal sinus is rarely necessary. Usually after performing an exenteration of the ethmoids and a Caldwell-Luc operation, the frontal sinus is provided with better drainage and ventilation through the frontal duct and exacerbations of infection are infrequent.

It seems to me that the importance of sinus disease as a primary cause of asthma is well shown by the effects of sinus surgery in asthmatic patients even after many years' duration. However, the results as recorded in the literature are not too encouraging.

TABLE 21

PATHOLOGIC CONDITION IN THE SINUSES AND OPERATIONS PERFORMED ON THE SINUSES IN 163 CASES OF ASTHMA

Pathologic Conditions	*Single*	*Bilateral*
Chronic sinusitis, ethmoidal	40	98
Chronic sinusitis, maxillary	44	108
Chronic sinusitis, sphenoidal	34	71
Chronic sinusitis, frontal	8	23
Chronic sinusitis, with nasal polyps	25	92
Pansinusitis	8	15
Cysts of the antrum	5	0
Operations		
Ethmoidectomy	34	91
Sphenoidectomy	11	36
Radical operation on the antrum (Caldwell-Luc)	37	64
Window resection of the antrum	7	0
Total number of operations on the sinuses	280	

Heatley and Crowe,[22] in a series of sixty-two operative cases, found fifty-three improved, but "only one case was enthusiastic enough to describe himself as cured" after three years. Rackemann and Tobey[23] studied ninety-one asthma patients whose sinusitis was treated surgically and reported 14 per cent cured, 46 per cent improved, 31 per cent unimproved and 9 per cent dead. Weille[24] stated that in his group of forty patients, whom he operated upon for sinusitis, only 50 per cent had a chance for relatively long-continued improvement in their asthma.

Schenck and Kern,[25] Vaughan,[26] Warner and McGregor[27] reported even less favorable results. It seems to me, however, that many of these reports are not clear as to the importance of associated sensitizations, the extent of the sinus disease, and the completeness of the removal of the diseased tissue from all of the sinuses.

Since 1935 three very complete studies of the results of sinus surgery have been made on asthmatic patients from the Allergy Division of Roosevelt Hospital. The first study, reported in 1935,[28] included 120 patients, one of whom had been followed for as long as three and a half years postoperatively. In 1936,[29] 173 patients operated upon during the previous five years were reviewed. Finally in 1941[30] I reported on 200 patients with a postoperative period of observation of six years. It was very interesting that the percentage of improvement in the asthma was almost the same in the three groups.

An intelligent analysis of the effect of sinus surgery on asthma must include accurate information as to the type of asthma, that is, whether due to infection, infection combined with sensitizations, or to sensitizations alone. Sinus disease in a patient whose asthma is due to house dust, pollens, animal danders or foods does not require operation to cure the asthma. In the second place it is necessary in the infective type of asthma to know how many sinuses are involved with disease and how complete was the operation. In other words, if both the ethmoids and antrums are involved an operation on either the antrums or ethmoids alone will not produce a good result. Likewise if both antrums are diseased and only one is operated upon there is no reason for thinking the patient will be improved. Complete elimination of diseased tissue as far as possible is absolutely necessary. For this reason I do not believe that the simple removal of a polyp or polyps with the snare or "making of a window" in an antrum is sufficient operative procedure.

One hundred and sixty-three asthmatic patients whose sinus disease was treated surgically have been followed postoperatively for one-half to thirteen years. They have all been studied as to the type of asthma and the completeness of the surgical procedures carried out. No results are reported with less than six months' follow-up because these results are too transitory; the effect of the anesthetic often produces a temporary relief from the asthma, while the removal of the infected sinus membranes may produce an immediate exacerbation of the asthmatic symptoms.

The infective group comprises eighty cases and the combined group, that is, infection plus sensitizations, eighty-three cases. The group in whom sinus surgery was considered complete contained 110 cases and the incomplete group fifty-three cases.

Tables 22, 23 and 24 analyze these groups carefully according to the various postoperative periods. The symbols +, ++ and +++ have been arbitrarily selected to designate the improvement in the asthma. The improvement in the total group or the sum total of ++ and +++ results was 64.4 per cent. This is not much below the figures reported in the three previous surveys.[28, 29, 30] In this group, however, I am including hospital outpatients who are more difficult to treat thoroughly or completely than private patients.

Several points should be stressed in the analysis of these tables. In the first place, it is quite obvious that there is a striking difference in the group who were operated on as completely as possible and the group treated incompletely: 76 per cent improvement as compared with 35.8 per cent. It is also observable that in the completely operated group the improvement increased with the duration of the postoperative

TABLE 22

Results of Surgery on the Sinuses in 163 Cases of Asthma

Postoperative Period, Years	*Cases*	+	++	+++
½ to 1	18	8	8	2
1 to 2	23	9	8	6
2 to 3	18	7	6	5
3 to 4	24	10	9	5
4 to 5	17	3	9	5
5 to 6	11	5	1	5
6 to 7	7	2	3	2
7 to 8	8	2	1	5
8 to 9	8	2	3	3
9 to 10	10	6	3	1
10 to 11	4	0	0	4
11 to 12	6	1	4	1
12 to 13	7	3	2	2
13 to 14	2	0	1	1
	163	58	58	47
Total of ++ and +++				105 or 64.4%

+ Indicates slight or no improvement
++ indicates definite improvement
+++ no asthma or a rare attack

TABLE 23

Results of Surgery on the Sinuses in 163 Cases of Asthma Based on the Completeness of Removal of all Diseased Tissue

Postoperative Period (Years)	*Complete Surgery*			*Incomplete Surgery*		
	+	++	+++	+	++	+++
½ to 1	4	5	1	4	3	0
1 to 2	6	7	5	2	2	2
2 to 3	0	6	3	7	0	2
3 to 4	5	7	3	6	1	2
4 to 5	3	9	5	0	1	0
5 to 6	3	0	4	3	0	1
6 to 7	2	2	1	2	0	1
7 to 8	0	1	2	2	0	2
8 to 9	0	3	3	2	0	0
9 to 10	2	3	1	4	0	0
10 to 11	0	0	3	0	0	1
11 to 12	1	3	1	0	1	0
12 to 13	1	2	1	2	0	0
13 to 14	0	1	1	0	0	0
	27	49	34	34	8	11
Total of ++ and +++		83 or 76%			19 or 35.8%	

+ indicates slight or no improvement
++ indicates definite improvement
+++ indicates no asthma or a rare attack

period of time. I believe that this is explained by the fact that there are secondary foci of infection in the cervical and bronchial lymphatic glands and the bronchial mucosa and that these secondary foci heal slowly after the removal of the primary focus. It is possible that the patients who did well immediately after operation and remained well never had these secondary foci; while on the other hand the patients who did not do well, even with increasing time, lacked the capacity to overcome these foci.

TABLE 24

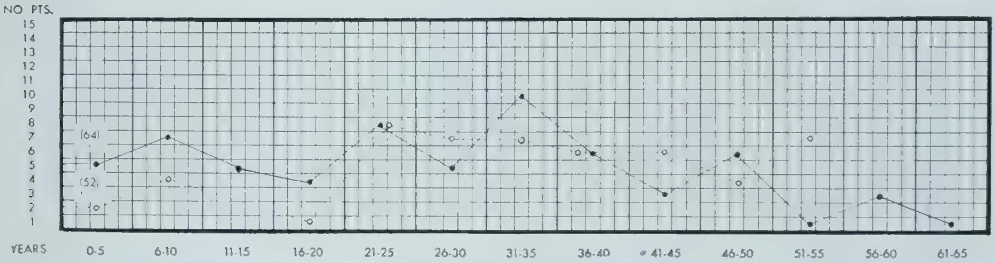
Results of Surgery on the Sinuses in 163 Cases of Asthma Based on the Type of Asthma

Postoperative Period, Years	*Infective Type*			*Combined Type*		
	+	++	+++	+	++	+++
½ to 1	5	4	0	3	4	2
1 to 2	8	3	2	1	5	4
2 to 3	3	5	3	4	1	2
3 to 4	4	4	2	6	5	3
4 to 5	3	1	1	0	8	4
5 to 6	4	1	1	1	0	4
6 to 7	2	2	1	0	1	1
7 to 8	2	1	2	0	0	3
8 to 9	1	2	0	1	1	3
9 to 10	5	2	0	1	1	1
10 to 11	0	0	0	0	0	4
11 to 12	0	2	1	1	2	0
12 to 13	1	1	1	2	1	1
13 to 14	0	0	0	0	1	1
	38	28	14	20	30	33
Total of ++ and +++		42 or 52.5%			63 or 76%	

+ indicates slight or no improvement
++ indicates definite improvement
+++ no asthma or a rare attack

In 1941[30] I reported in the study of 200 cases of asthma which were operated upon that twenty-seven of the patients had a "window" resection or an antrotomy with only 40 per cent improvement in their asthma. On the other hand, nineteen patients who had had previous antrotomies were operated upon radically and a 79 per cent improvement was obtained. Ninety-four cases who had primary radical antrum operations showed a 75.5 per cent definite improvement in their asthma. These figures indicate that the antrotomy operation does not completely eliminate the infection in the membranes. I have noticed after antrotomy that frequently the "window" becomes blocked by polyps, so that it does not function, and that upper respiratory infections are more frequent, necessitating more local treatment of the sinuses and, of course, producing exacerbation of the asthma. Patients who have had the necessary surgery completed frequently go through the upper respiratory infections without any or only a slight flare-up of their asthmatic symptoms.

Referring again to the 163 cases analyzed in Table 24, it is seen that the results are better in the combined type of asthma than in the infective type. In this group the infection is often a secondary factor and, in addition, all of these patients are treated with injections of the indicated allergens as well as by the proper elimination of the allergens when possible. Injections of house dust have not only helped to maintain prolonged freedom from asthma, but have in many cases helped to prevent the recurrence of nasal polyps. Practically all of the patients of both groups were treated with autogenous vaccines made from cultures of the infected sinus membranes removed at operation. In addition all extranasal infections with molds (fungi) or spirochetes and of course tuberculosis should be treated; infected teeth, tonsils and adenoids should be removed. A few of the patients who improved but moderately after a complete sinus operation showed striking improvement after having an ovarian or uterine tumor or an infected gallbladder or appendix removed.

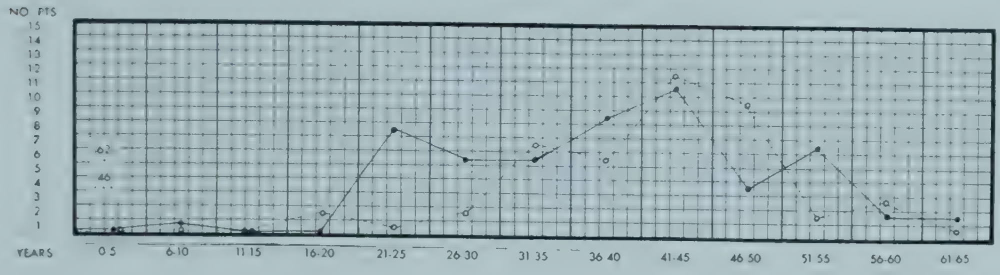


unbroken line represents slight or no improvement (+)
broken line represents no asthma or a rare attack (+++)

Fig. 12.—Graphic studies of 163 cases of asthma with diseases of the sinuses treated surgically. Age at onset of asthma.

Figures 12, 13 and 14 show graphically an analysis of the best and the poorest results in the surgically treated group of 163 cases of asthma. It is difficult to draw absolute conclusions but a few facts seem evident. In the first place, in Figure 12 it is seen that in the total +++ group of fifty-two cases there are only seven patients whose asthma began before twenty-one years of age, while in the + group of sixty-four cases there are twenty-one patients. The greatest number of patients in the +++ group began having asthma between the ages of twenty-one and thirty-five, but there is another peak from fifty to fifty-five years. The question of duration is also important as many of the older patients had had their asthma a shorter time.

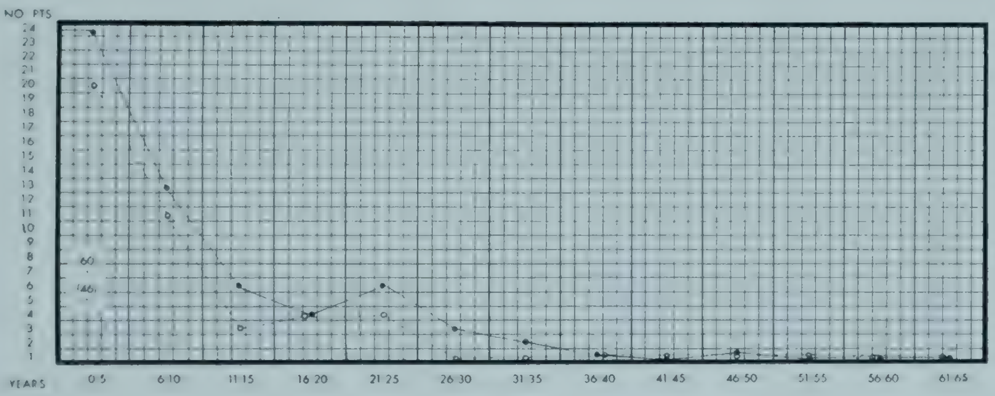
Figure 13 analyzes the poorest and best results from the standpoint of age at operation. It is readily seen that the best results are obtained in the patient from thirty-one to fifty years of age.



unbroken line represents slight or no improvement (+)
broken line represents no asthma or a rare attack (+++)

Fig. 13.—Graphic studies of 163 cases of asthma with diseases of the sinuses treated surgically. Age at operation.

Figure 14, which analyzes the poorest and best results as far as duration of the asthma is concerned, is very interesting. Of our best results, comprising forty-six cases, practically 50 per cent had asthma less than five years; while an additional 25 per cent had asthma not more than six to ten years.



unbroken line represents slight or no improvement (+)
broken line represents no asthma or a rare attack (+++)

Fig. 14.—Graphic studies of 163 cases of asthma with disease of the sinuses treated surgically. Duration of asthma.

It seems from these charts that a patient whose asthma began between twenty-one and thirty-five years of age and has been present not longer than ten years and preferably less than five years, and who is between thirty-one and fifty years of age at the time of operation, has the best chance to obtain a satisfactory result.

Summary

The incidence of sinus disease in asthmatic patients, the type of tissue change, the bacteriology of the diseased membranes, and the results of sinus surgery show that sinus disease is a very important cause of asthma. Any thorough and intelligent treatment of asthma requires that careful consideration be given to pathologic conditions in the paranasal sinuses. Special diagnostic studies such as the use of the nasopharyngoscope and the injection of radiopaque solutions into the antrum are necessary in all doubtful cases of disease of the sinuses.

In order to estimate correctly the effect of surgical treatment of the sinuses on asthma two points should be considered: (1) whether there is infection alone or infection associated with an allergy of the skin-sensitive type and (2) whether the diseased membranes have been completely or incompletely removed by operation.

Complete surgical elimination of the sinus infection produces a greater percentage of improvement in asthma than incomplete surgical treatment. Immediate improvement should not be expected and follow-up studies have shown that with increasing postoperative periods of time steadily improving results are obtained. I believe that this is due to the gradual elimination of the secondary infections in the cervical and bronchial lymphatic glands and the bronchial mucosa. It is possible that the patients who do poorly lack this capacity to overcome their secondary foci of infection.

Surgical treatment of the sinuses cannot be expected to produce improvement of the asthmatic condition if extranasal infections and associated allergies are not treated properly. Autogenous vaccines are considered important in the treatment of infective asthma.

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Section III

ALLERGY OF THE UPPER RESPIRATORY TRACT

In the sum total of diseases involving the nasal region of the upper respiratory tract the infections per se and the allergies, including bacterial allergies, are preeminent. There seem to be no data which provide information as to their relative frequency, but from the standpoint of the patient's discomfort and the implication of eventual asthma there is no doubt but that the allergies are very important, for once started there is little tendency to spontaneous cure. For purposes of presentation allergic rhinitis is divided into seasonal (hay fever) and perennial (vasomotor rhinitis and hyperplastic rhinitis). While this nomenclature is not strictly correct or satisfactory from all angles it coincides essentially with general, customary and clinical usage.

10. Allergic Rhinitis: Seasonal (Hay Fever—Pollinosis)

ALBERT VANDER VEER

Introduction

IN THE great majority of cases seasonal vasomotor rhinitis or hay fever is due to a hypersensitiveness to pollens. It is not necessary to review the history of the development of our knowledge of this condition beyond mentioning the names of Bostock, Blackley and Dunbar who were among the earliest investigators. Hay fever is, of course, an allergy and it must be remembered that in an allergic person the entire mesenchyme is hypersensitive but in varying degrees for each tissue. Where an allergen comes in contact with hypersensitive tissue edema occurs and the location of the tissue displaying the most acute sensitiveness (called the shock tissue) determines the symptoms and therefore the name that is given the disease. If the shock tissue happens to be in the mucous membranes of the eyes, nose and throat the disease is called allergic coryza, if in the bronchial mucous membrane, asthma, while less frequently other shock tissues, as those of the gastro-intestinal tract or skin, may play the dominant role.

Any condition which recurs periodically at about the same time of the year should raise the suspicion that it may be an allergy, although not always due to pollen. An interesting example of this is the occurrence of asthma in a large number of people during June and July near Lake Erie. Parlato[1] proved this to be due to the scales from the wings of the caddis fly which migrates inland in large numbers at this time of the year. In a case reported by Sternberg[2] the chief complaint was lassitude occurring periodically during the ragweed season. The patient gave a marked skin reaction to ragweed and his symptoms were relieved by injections of ragweed extract. Cases of seasonal dermatitis are fairly common due to skin sensitiveness to the leaves and stems, and occasionally to the pollens, of grasses, ragweed and other weeds. Gastro-intestinal disorders have been observed in patients treated orally with capsules of pollen for hay fever.

While the majority of hay fever patients complain chiefly of sneezing and blocking of the nose, a few are bothered more by tearing, edema and itching of the eyes and nasopharynx. Usually both eyes and nose are affected in varying degrees and about 30 per cent of untreated hay fever patients develop seasonal asthma. In these the asthma usually begins about a week or two after the season starts and is apt to continue for several weeks after the pollen has disappeared from the air. Rackemann[3] has noted that many cases of chronic perennial asthma started as seasonal fall asthma which, if untreated, tended to prolong itself later and later each year until it finally became perennial. This furnishes a valid argument for the early and thorough treatment of even mild hay fever to prevent the development of more serious trouble later. Asthma due to pollen is occasionally seen without ocular or nasal symptoms but this is rare.

Etiology

While pollens are by far the most common cause of seasonal vasomotor rhinitis and asthma, other factors must be considered as possible causes, among these being molds, insects and foods.

Pollens. The following remarks are particularly applicable to that section of the United States lying east of the Mississippi River. West of the Mississippi the problem is somewhat different and there are more local variations.

The pollens of importance in the causation of hay fever are those which are air-borne, for those disseminated by insects rarely come in close contact with human beings, hence do not cause trouble even in those sensitive to them. Any pollen-bearing tree, flower or weed which has developed color or odor has done so to attract insects for its pollen dissemination and its production is relatively small. The inconspicuous weeds and grasses must depend on the wind to distribute their pollen and must produce tremendous quantities of it, hence they are of greater interest and significance as factors in nasal allergy. It is true that many people give skin reactions to the pollen of asters, cosmos, dahlias and other flowers (not to roses or lilies), and they will show symptoms if brought in close enough contact to the pollen, but because the pollens of these flowers are heavy and sticky and do not travel far this rarely happens and treatment is seldom necessary. Occasionally florists, gardeners and those who must handle and arrange flowers have been given injections of the proper extracts with satisfactory results. It must be borne in mind that flowers can cause hay fever, as this will explain some cases of fall hay fever which do not clear up when adequately treated with ragweed alone and which tend to persist late in the fall when all air-borne pollen has disappeared from the air. The clue in these cases is that the patient is more uncomfortable inside than outdoors and removal of all flowers from the house usually relieves his symptoms promptly.

Pollen Seasons. Three pollen seasons, designated as Spring, Early and Late, are commonly recognized. The *Spring Season* extends from early March to June and is due to the tree pollens. Chief of these in the order in which they appear are elm, poplar, ash, beech, birch, oak, sycamore and hickory. Of these oak is the most important and widespread. Less important are alder, hazel, maple, pecan (in Georgia and northern Florida) and cedar (in Texas and Bermuda). Pine is a heavy pollen producer, but cases clinically sensitive to it are rare and the same holds true for the other evergreens, spruce, balsam and hemlock, although Christmas trees, as they become dry indoors, may bother a few people.

This list does not cover every tree pollen which is a potential cause of trouble but it does include the great majority of them. Reports have been published of isolated cases due to mulberry, ailanthus and many other pollens, but they are relatively infrequent. The pollinating season for individual trees is quite short and depends on whether their location is sheltered or exposed. Any one tree may give off a tremendous quantity of pollen but only for a very few days. The Spring Season may be greatly influenced by the weather, both as to time of onset and quantity of pollen produced.

If a patient is sensitive to one species of a genus he will react to all the species of that genus and also will be protected by an extract made from any one of the species against all the others. An extract of red or white oak will protect against all the oaks, but of course will not protect against birch or hickory. This simplifies the problem of treatment considerably.

The *Early Season* begins in mid-May with the pollination of plantain and sorrel which is at its height the last week in May and the first week in June, rapidly diminishing thereafter, although plantain pollinizes scantily even into August. The grasses start pollinating feebly in mid-May, continuing until the middle or end of July, but rarely cause clinical symptoms until May 30. While there are a dozen or more common grasses as sweet vernal, June, low spear, red top, orchard and timothy, all are closely related and a patient reacting to the pollen of one will react to all. Treatment with pollen extract of one species will protect against all the rest. The heaviest pollen producers are orchard grass, whose peak occurs about the 10th of June, and timothy, which is heaviest in early July. As timothy pollen is the easiest to procure it is used at the Roosevelt Hospital Clinic for treatment in all grass-sensitive cases. Bermuda and Johnson grass are the commonest in the South but are almost nonexistent north of Georgia. Patients are frequently sensitive to both grass pollen and plantain or sorrel and must be treated with extracts of both as there is no cross-protection. Clinically a patient whose symptoms do not begin until June 1 is apt to be a pure grass case, while if the onset is mid-May, with a good deal of trouble before June 1, he is almost certainly a plantain case with or without grass sensitization combined.

The onset of pollination for plantain, sorrel and the grasses is less apt to be influenced by weather conditions than it is for the trees. The onset is more variable than that for ragweed and the total amount of pollen in the air is much less than in the late season. Corn pollen is rarely the cause of hay fever, although it is produced abundantly and many people give a skin reaction showing they are potentially sensitive. Corn pollen is heavy and sticky with little wind dissemination and the few clinical cases I have observed were in farmers actually working in corn fields. Favorable results are obtained by treatment with corn pollen extracts.

The *Late Season* begins early in August and lasts until the first frost or even later. It is well known that the chief interest at this season lies with the ragweeds, high and low. They are the cause of more hay fever than all other pollens combined. As the United States is the favorite habitat of ragweed, it has the dubious distinction of harboring more hay fever victims than all the rest of the world together. High ragweed begins to pollinate the middle of August, reaching its peak about the 25th to the 30th. As its pollination begins to decline low ragweed takes over and reaches its height the first two weeks of September, continuing until frost. The date of onset is less influenced by weather than that of the trees and grasses, but naturally varies somewhat with rainfall, latitude and mean temperature.

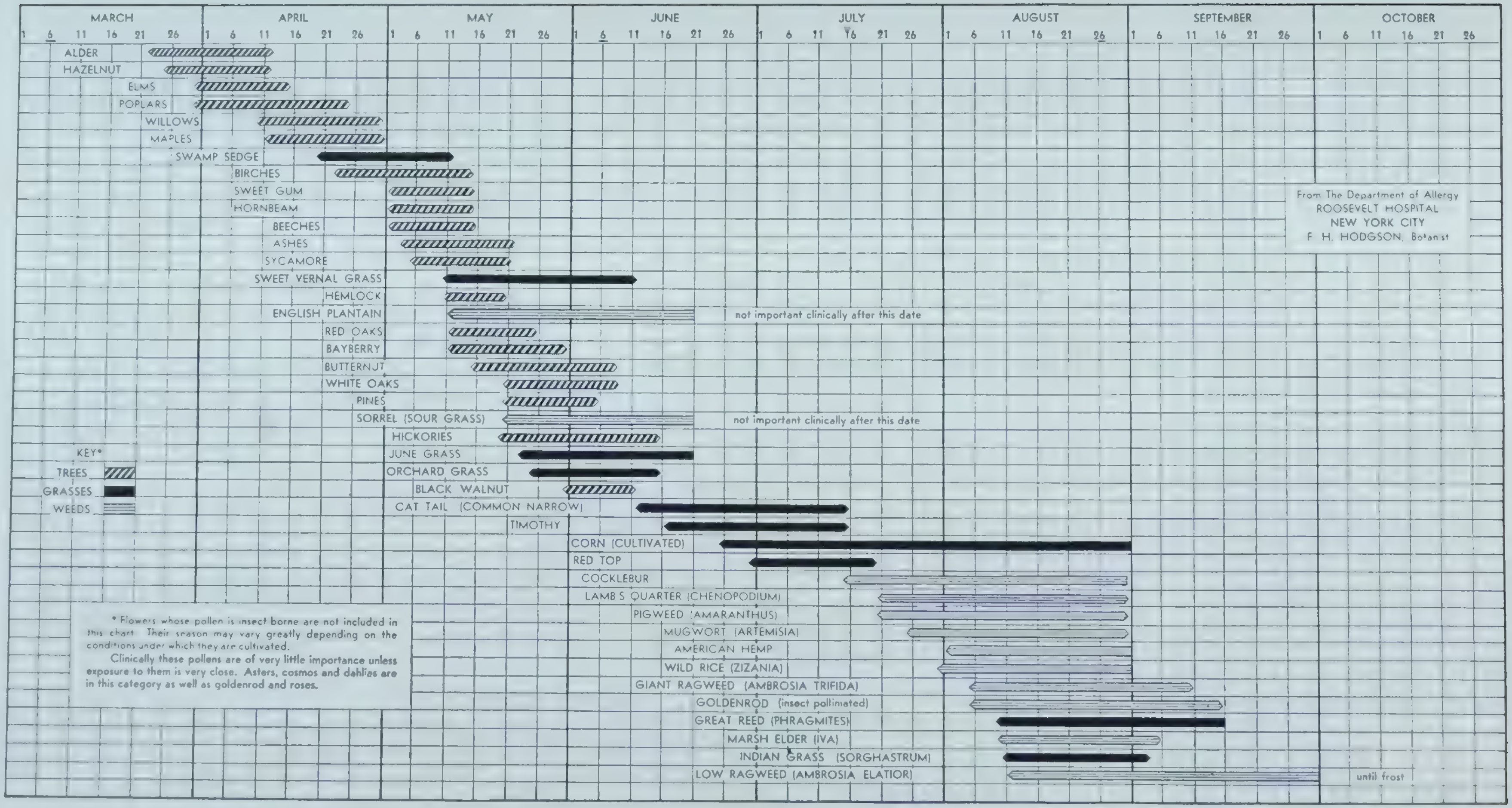
West of the Mississippi there are other weeds which rival the ragweeds in importance. Chief among these are the various amaranths (pigweed or tumbleweed), artemisias (sages), chenopods (lambs quarter), ivas (marsh and burr elder), cockleburs, Russian thistle and hemp. Some of these have gradually extended their domain east of the Mississippi and are complicating the therapy problem to some extent. Also less common are wild rice, great reed, Indian and marram grasses and the sedges and sugar beet, which are more in the nature of local problems.

While it is sure that everyone east of the Mississippi will be exposed to ragweed except in a few isolated areas, the distribution of the other pollens is much less general, so that if a patient is sensitive to Iva and some of the other pollens and gives reactions to them (as he often does) it is a difficult question to decide whether to treat for them or not. The ragweed extract does not protect against the other weeds in all cases, but as the total dose of extract a patient can take is more or less limited, the addition of Iva and one or two more extracts to a mixture decreases the amount of ragweed and thus reduces the protection to the more prevalent allergen. Even an accurate survey of the surrounding country to determine the presence or absence of other weeds would not help greatly because patients range over a considerable territory in summer and pollen travels hundreds of miles. If a patient has some hay fever the physician cannot prove whether he lacks immunity for ragweed or has encountered other pollen for which he has no protection. This may explain why results in the treatment of Late hay fever are less satisfactory than with the Spring and Early types of hay fever. Another reason lies in the fact that there is a far greater amount of pollen in the air during the ragweed pollen season. There is one clue which may help to decide whether other pollen extracts in addition to ragweed should be used, namely, that Iva, chenopod, artemisia and others previously mentioned start a little earlier than ragweed, and if hay fever starts late in July or very early in August before the ragweed has begun to bloom, one may well suspect some of the other Fall weeds (Chobot[4]).

A difficult problem is presented by a substantial group of patients who display their severest symptoms from the middle of September to the middle or end of October when all known pollens and molds are declining or are absent from the air. Many of these do give reactions to ragweed and are improved during August and September with treatment, then get worse instead of better as the ragweed pollen decreases. Others give little or no reaction to any of the other pollens or molds. This problem has not been satisfactorily solved, but there are several possible explanations. In the first place the trouble may be due to sudden changes in temperature acting on mucous membranes already irritated by pollen, and this may stir up a latent sinus infection. Secondly, many people return to the city from the country about this time and move into a renovated or redecorated apartment and come in contact with rugs and draperies which have just come from storage. Fresh paint, camphor and chemicals used in mothproofing are prone to cause nasal irritation. Thirdly, children starting school are apt to "catch cold" and bring infection home to the family. Finally, fresh flowers as dahlias, asters and chrysanthemums are used for house decoration. In any event the house or apartment should be thoroughly cleaned and all fall flowers removed as the dried pollen indoors may cause symptoms much more easily than in an open summer house or a garden. These measures will relieve some of the patients of this group, but there must be other undiscovered factors as many people have the same difficulty year after year at this time. The symptoms are just as apt to be bronchial as nasal and continue late into the fall. A fair percentage of this group show chronic sinus infection and attention to this is very important.

Pollen Chart. While it is impractical for every physician treating hay fever to have a trained botanist at his command, it is possible and necessary to have an accurate pollen chart for his section of the country. The chart here shown (Fig. 15) was made by Mr. Fred Hodgson of Montclair, New Jersey, and is based upon daily pollen surveys over many years. It is strictly applicable to the general region of New York City and its environs, New York, New Jersey, Connecticut and Eastern Pennsylvania. Similar surveys have been made by many observers throughout the United States (chief among whom are Durham[5, 6] and Wodehouse[7, 8]) and pollen charts are obtainable for almost any section. The Hodgson chart lists the onset and offset of pollination of all the important hay fever producing trees, grasses and weeds in the eastern United States.

CHRONOLOGY OF AIR-BORNE POLLENS



From The Department of Allergy
ROOSEVELT HOSPITAL
NEW YORK CITY
F. H. HODGSON, Botanist

* Flowers whose pollen is insect borne are not included in this chart. Their season may vary greatly depending on the conditions under which they are cultivated.

Clinically these pollens are of very little importance unless exposure to them is very close. Asters, cosmos and dahlias are in this category as well as goldenrod and roses.

Fig. 15.—Chronology of air-borne pollens.

While the periods may vary a little from year to year, depending on the weather, the variation is not marked and the order in which pollination occurs is unchanged.

The use of the chart is very simple. The onset and cessation of the patient's hay fever are checked against it and all pollens beginning and ending within that period may be suspected, while all falling outside that period cannot be causal factors. For instance, if the patient's hay fever begins in mid-May and is over by the end of July, plantain, sorrel and the grasses would naturally be suspected but not ragweed. This may seem elemental and yet I have seen patients with such a history being treated with ragweed extract, naturally without any relief. This check on clinical history is most important, as will be seen later when I shall discuss testing, as a patient may give skin reactions to many pollens and yet have clinical symptoms from only one or two of them.

Daily field surveys and reports made each year by a trained botanist are helpful as they enable one to judge what hay fever excitants are abundant in the neighborhood on any given day and whether the amount of pollen is heavy or light.

Pollen Counts. Daily pollen counts are helpful but have some limitations. They must be made by someone with considerable experience, for while it is easy to tell ragweed from grass pollen it is not easy, except for an expert, to tell ragweed from some of the other fall pollens, nor one grass from another and it is just this information that is important. Also, pollen reports are apt to be like yesterday's newspaper, for by the time they arrive the patients have evidenced by their symptoms whether the count that day was high or low. Pollen counts do enable one to know at the end of the season whether it has been a light or heavy pollen year, when the peak periods have occurred and also what areas are safest for hay fever sufferers. A trained observer can determine what pollens are particularly abundant in any given area and this can be checked against the patient's history and positive tests. In general, the heavier the pollen count the poorer will be the results of treatment and vice versa. This is well demonstrated in Figure 16 covering the five years from 1930 to 1934. In 1930, with a total pollen count of 1100, the percentage of satisfactory results was 84, while in 1931, with a total count of 2600, the percentage of satisfactory results fell to 70. Hodgson,[9] whose experience in pollen surveys and pollen counting extends over a period of thirty years, maintains that daily field surveys give a more accurate idea of the different pollens encountered in a given area and that pollen counting should be used merely as a supplement to this.

The lower part of Figure 16 records the percentage of 400 treated cases that had "satisfactory" results during each of the five years, 1930 to 1934 inclusive. The solid middle line shows the general average, the lower (dash) line those treated preseasonally and the upper dotted line those who received perennial treatment. The results with the perennial cases are about 10 per cent better than those treated preseasonally.

The upper part of the chart gives the total pollen count each year for the same five years and taken in conjunction with the lower chart shows that as the pollen count rises, as in 1931, the percentage of the satisfactorily treated cases falls and vice versa.

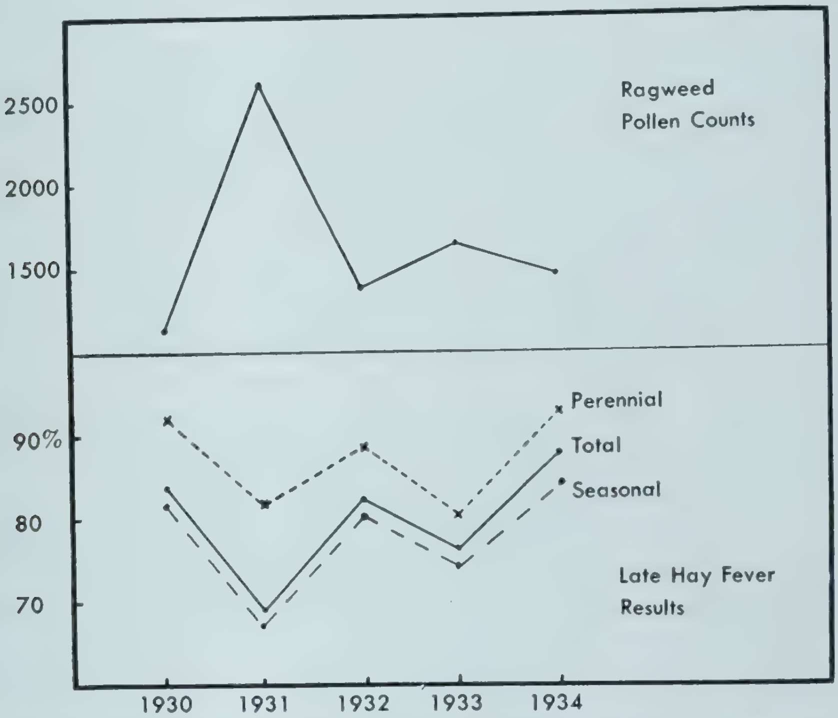


Fig. 16.—A comparison of the total annual pollen count with the results of pollen therapy (ragweed).

Molds. The study of molds is rather discouraging as it is such a vast field in itself, but there are a few facts which may be of help. Sensitiveness to molds is more apt to cause asthma than hay fever, is most apt to occur in children, and rarely occurs except in combination with sensitivity to pollens, particularly ragweed. The different molds have no such definite season as the pollens, but all grow more profusely in hot, wet weather and particularly in humid climates. While there are thousands of different species, a dozen to twenty of the more common ones have been studied principally. Chief among these is Alternaria whose spores account for more cases than all the others combined. Next in importance is Hormodendrum, and less frequently observed are Aspergillus (with several species), Dematium, Cephalothecium, Cladosporium, Helminthosporium, Monilia albicans, Mucor, Penicillium and Trichoderma. It takes some time to grow the spores in sufficient quantity but the extracts are not too difficult to make and are standardized in the same way as pollen extracts (protein nitrogen unit). They give skin reactions in sensitive patients and can be used successfully in treatment.

When combined with a sensitiveness to pollens, the clinical history may be quite confusing. Symptoms which would make one suspect a mold complication in a pollen case are: exacerbations in muggy weather even when there is no pollen in the air, irregular season not corresponding to that of any important pollen (as the end of July and early August) and the poor result obtained if the patient is treated with pollen alone. Bell[10] has reported a few cases of pure Alternaria sensitization in children, but this is the exception rather than the rule. In our clinic hay fever and asthma patients are routinely tested with a combined mold extract. If this is positive, tests for the separate molds are done. If negative, further tests are not indicated unless results are unsatisfactory with pollens alone during that season.

In the farming country of the Middle West, rusts and smuts are the cause of seasonal trouble, and cases have been reported by Feinberg,[11] Prince,[12] Morrow[13] and others. Historical credit for first calling our attention to the importance of molds, rusts and smuts belongs to van Leeuwen[14] of Holland who wrote about them as early as 1924. Unfortunately, little attention was paid to his work in this country until 1930.

Insects. In certain localities the scales from the wings of insects may be a definite cause of seasonal trouble, more often asthma than hay fever. A careful study was made by Parlato[1] on the caddis fly which swarms in huge numbers a few miles inland from Lake Erie in June and July. He observed a fairly large number of patients who suffered from asthma chiefly during this period of the year, tested them with an extract of wing scales, treated those who gave reactions and obtained satisfactory results in a large percentage of the cases. Figley[15] at about the same time reported four cases of hypersensitivity to May fly emanations. I have tested many of my patients with moth scale extracts and obtained a number of skin reactions (almost never occurring alone), but have had very few satisfactory results from treatment or improvement in results when the moth extract was added to pollen extracts. From this experience I have concluded that while these patients may be sensitive to moths their exposure to them along the Eastern Seaboard must be very slight.

Foods. From the beginning of our knowledge of hay fever it has been claimed by some that diet is an important factor in its causation, but I am convinced that this is rarely the case. A few people sneeze when they eat asparagus, melons or peaches. More will develop urticaria or intestinal symptoms from berries, corn, tomatoes or shellfish. Most of these people know their sensitivities and regulate their diet accordingly. Occasionally good results have followed when seasonal fruits and vegetables are omitted from the diet of a patient who is not doing well on pollen injections, and possibly the milk from cows in pasture may be different from that of cows fed on hay in the barn in winter. Unfortunately, the average food faddist advises omitting proteins as meat, fish and eggs, which may be eaten with impunity in the winter, thus limiting the diet to fruits and vegetables, which are the very things that may cause trouble. This is neither rational nor wise.

Diagnosis

History. For the successful treatment of hay fever a careful and accurate history is of the utmost importance. It will be found that it is easier to let the patient tell his own story first briefly, and then fill in the important facts by direct questioning. First find out the approximate dates of the onset and cessation of trouble, the period of maximum intensity, duration in years, whether it is increasing or decreasing in severity and whether there have been any free years. One should also find out where the patient usually spends his time during the season, whether the symptoms are worse indoors or outside and whether at night or during the day. Any special facts should be noted such as exposure to animals or dusty bedding and old feather pillows or exceptional contact with pollens, as when working on a farm or in a garden. Occasionally it will be found that hay fever designated as seasonal is really environmental, that is, the patient may be in the habit of going to a certain place at about the same time every year and the trouble may be due to animal dander or dusty bedding rather than to pollens. In such a case the period of trouble will not correspond exactly to any particular pollination season, but rather to the dates of arrival and departure, and the symptoms will be worse at night and indoors rather than during the day and out of doors where the exposure to pollen is much greater.

Histories as first taken are apt to be inaccurate and must be revised later as the patient's memory is refreshed. It is common knowledge that most hay fever begins in the middle of August and some people will make their history conform to the average, whereas more careful questioning will bring out the fact that their trouble really begins in late July or early August which may change the whole picture. I have even met patients who gave a typical history of Late hay fever, but positive tests to grass pollen and more careful questioning later brought out the fact that their chief trouble was in June and July and that by September they were all right.

The history should also state whether the worst symptoms are in the eyes or nose and if asthma is a complication. The physician should also know if there has been any previous treatment, if so the result and whether marked local or constitutional reactions have occurred. Some people are much more apt to develop reactions than others and advance information on this point will make one more cautious with the dosage.

After the first year of treatment it is possible to determine the season with greater accuracy from the weekly notes. In special cases the patient may be given a card on which he checks his daily report, noting the date of onset and cessation of symptoms and periods of maximum severity. From this card can be made a simple individual chart which can be checked against the standard pollen chart, and this will give a pretty good idea of the pollens causing the trouble. I do not, of course, advise making such a chart for every patient, but in puzzling cases it may be very helpful. This is particularly true when there is a complicating perennial vasomotor rhinitis and the skin tests to the weaker pollen dilutions are negative or slightly positive. The pollen complication may be missed entirely unless the chart shows that for several years there have been exacerbations at the same time in the summer and that this corresponds to a definite pollen season. This will induce one to continue the tests with stronger extracts and add whatever treatment is indicated, frequently changing a poor result into a good one.

The importance of history and clinical symptoms over mere positive skin tests should be emphasized. Many patients will give positive tests to a dozen or more different pollens and yet have clinical symptoms from only one or two of them, and these may not necessarily be the ones giving the most active reactions. After all it is the hay fever one wants to relieve, not the skin tests. This point is covered more fully under the subject of testing (p. 194).

While more than half of the patients will give a history of straight Late hay fever, they may have a combination of any two or all three seasons. The usual combination is Early and Late hay fever, that is, beginning May 15 to June 1 and lasting until the end of July, then a comparatively free period for three weeks with a recurrence from mid-August to frost. This is strong evidence that the trouble is due to grass pollen and ragweed combined. If the trouble begins in mid-May, plantain and sorrel must be added to the list of suspects. If the onset is in March, April or May the tree or trees responsible must be detected, and if there is a free period in June and July the grass pollen can be ruled out, while if the cessation is at the end of July ragweed cannot be at fault.

In general, it may be said that the Spring hay fever is less constant, less severe, usually showing a few bad days during a high pollen count, and is much easier to control. The Early hay fever also shows good results from treatment, the only real trouble being in early June from orchard grass and plantain and in July from timothy. The Late hay fever is the most constant and distressing, the hardest to control and is the most apt to develop into asthma.

Testing. *Skin Tests.* After taking a careful history, one should proceed with testing. This is done preferably by the intradermal method rather than the scratch method as it is more accurate, although more apt to cause constitutional reactions. With proper precautions and some experience these can usually be avoided. The object of the tests is to determine to what pollens a patient is sensitive and the degree of sensitivity in order to graduate the doses for treatment. It must be borne in mind, however, that the activity of the reaction has no bearing on the severity of the symptoms. In other words, a patient may give a marked reaction to 10 units of timothy extract and a slight reaction to 1000 units of ragweed, and yet suffer clinically from mild Early hay fever and severe Late hay fever. The tests and clinical history must be evaluated together to get a true picture of the treatment needed.

Testing extracts are usually made in strengths of 10, 100 and 1000 protein nitrogen units per milliliter. Stronger and weaker extracts may be needed in special cases. The extract is introduced into the superficial layer of the skin through a 26 gauge needle ⅜ inch in length. One-fortieth milliliter or even less of the extract is sufficient for a test. The needle should be held parallel to the skin and should not pierce the outer layer. The inexpert tester may puncture the outer layer and then try to bring the point back up again into the outer layer, causing unnecessary discomfort and a resulting negative or confusing test. With a little practice it is easy to make the test intradermally and if this is done it is almost painless.

The usual procedure is to start with the 10 unit strength of each pollen extract, putting in six tests at a time and using the outer side of the arm or thigh. The tests should be placed an inch apart and if in the arm (which is preferable) space should be left between the shoulder and the upper test to apply a tourniquet if a constitutional reaction should develop. My custom is to put the first row inside and ten minutes later a second row of six is introduced an inch further out and staggered. Ordinarily only three rows (eighteen tests in all) are put in a patient at one visit. Of course, if several tests in the first or second rows give very marked reactions and the patient appears to be on the verge of a constitutional reaction no further tests are done that day.

The reason for starting with the 10 unit strength is that it is wise to get a general idea of the sensitivity of the patient first and try not only the pollens suspected from the history but as many more as possible to find out if the patient is potentially sensitive to other pollens which may bother him clinically later in life. Extracts of house dust and the combined molds are also tested routinely. After obtaining this general survey the testing is continued on another day, using the 100 and 1000 unit strengths (as the case demands) of the pollens which are thought to be the cause of the patient's hay fever (from history and previous tests). In this way one tries to gauge roughly the degree of sensitivity, the doses that the patient will need for his protection and those he will be able to take safely.

Tests are graded as *marked* (showing redness, itching and having pseudopods), *moderate* (redness and itching but no pseudopods), *slight* and *negative*. These are sometimes qualified as marked plus or minus, moderate to marked, and slight to moderate. A marked reaction usually signifies sensitivity of clinical importance; moderate and slight reactions call for investigation with stronger extracts as they may or may not mean clinical sensitivity. The patients are divided roughly into four classes as to sensitiveness, depending on the strength of extract which is required to produce a marked reaction. If this can be elicited by the 10 unit strength the patient is classified as "A" or very sensitive. If slight or moderate to 10 units but marked to 100 he is called "B" or average, while if it requires 1000 units to produce a marked reaction he is put in class "C" or less sensitive. Patients who give only moderate reactions to 5000 or 10,000 units are in class "D," relatively insensitive.

An important point to be kept in mind in regard to skin tests is that a reaction does not always mean clinical sensitiveness as shown by hay fever or asthma and often does not call for treatment. This positive skin test may be induced long before there are symptoms in the eyes, nose or bronchial mucous membrane and may be retained long after the other tissues have become clinically insensitive. It is rare indeed to find a patient who reacts only to one pollen even though one pollen is the sole cause of symptoms. Usually he gives a stronger reaction to this one pollen (nor is this either an invariable rule), but is apt to react also in lesser degree to half a dozen others. Some time later his clinical sensitiveness may catch up with his skin reactions, or these may be left-over signs of previous trouble. Then, too, his positive skin tests may denote hay fever limited to a few days of minor symptoms at the height of the pollen season, so slight that he remembers them only after careful questioning. Treatment should be instituted only if positive tests confirm a positive history, but the general preliminary testing may give some valuable advance information. If a patient is treated with an extract of every pollen to which he gives a skin reaction he will have a very poor result.

Another important point to remember is that it takes two factors to produce hay fever, a hypersensitive person and exposure to the pollen to which he is hypersensitive. If a patient reacts to ragweed and expects to live in Europe (where there is no ragweed) it is foolish to treat him with ragweed extract. If he lives in the East and reacts to hemp and Russian thistle as well as to ragweed one should concentrate on the latter, as he will not be exposed to the other two unless he moves West and then he will require an entirely different mixture.

Eye Tests. Opinions as to the value of the eye reaction vary considerably among different observers. Theoretically this test should be of great value and it may be when pure pollen is used, as this is the same antigen as that which causes the hay fever. When diluted extracts are used the results are less conclusive. The extract is merely dropped on the conjunctiva and does not come in as close contact with the sensitive tissue as it does when introduced intradermally, hence it requires a much stronger extract to produce a positive eye than skin test. In my own experience the eye reaction parallels the skin test in the great majority of cases, that is, if the skin reaction is marked to a 10 unit extract the eye reaction may be positive to 100 or 1000 unit dilution, while if it takes 1000 units to produce a marked skin reaction it may require 5000 to 10,000 units to produce a positive eye reaction, or more often it may be negative. It would be helpful if the eye reaction were positive only in patients with clinical hay fever and negative in all those who do not have hay fever, but this is far from the rule. I have even seen one patient who gave marked skin and eye reactions to a 10 unit timothy extract and a moderate skin and slight eye test to 1000 unit ragweed extract, but complained only of Late hay fever. Some observers claim that the eye sensitiveness diminishes as the patient's protection rises and hence is a very valuable guide to treatment. I am not at all convinced of this and feel that there is rarely any need of supplementing the skin tests with eye tests.

The test itself is very easy to perform, simply by dropping a little of the ordinary testing extract in the inner canthus of the eye with the regular testing syringe. It is wiser to remove the needle from the syringe, particularly with children, as otherwise a sudden jerk might cause damage to the eyeball, but if care is used and the needle held at least an inch away and the extract squirted in even this is not necessary. A reaction may appear in from one to five minutes with reddening and itching of the caruncle and conjunctiva often associated with sneezing. Following a reaction it is well to instill an eye drop (the formula for which is under Treatment, p. 206) in the reacting eye, as otherwise the reaction may cause discomfort.

Extracts. The number of pollen extracts one should have on hand for testing and treatment varies according to the thoroughness with which one intends to pursue the subject. For the general practitioner a dozen or so are ample. These should include ragweed (high and low mixed), timothy (covering all the grasses), plantain, sorrel, oak and birch as the most important. To these may be added elm, poplar, ash, beech, sycamore, maple, hickory and some of the fall pollens as amaranth, artemisia, cocklebur, chenopod, Iva, and corn. If one plans to become an expert the list may run up to a hundred or so to take care of the lone patient who has a mulberry tree in his back yard or the fastidious gentleman who wants to wear a cornflower in his buttonhole although it makes him sneeze. Among the flowers the most important are aster, cosmos, dahlia, chrysanthemum and possibly goldenrod (if one can procure any pollen) as many people insist on being tested with it. Daisies, dandelions and roses are of little importance and the pollen is usually unprocurable. When one considers that important extracts should be made up fresh every year and the less important ones at least every two or three years, the difficulty of treating every rare case that comes along will be realized. Different sections of the country have their own local problems, such as the mountain cedar in Texas and pecan trees in Georgia and northern Florida. Incidentally, cedar is about the only hay fever-producing pollen occurring in Bermuda. For methods of making combination extracts see page 201.

Non-Skin-Reacting Group. A group of cases which has caused debate for many years is that in which the patients give a history of trouble in summer but give no or slight skin reactions to the strongest pollen extracts. Should they be treated or not? My own feeling is that if the patient has a clinical history of hay fever or asthma, corresponding fairly well with a definite pollen season, and gives even a slight reaction to a 10,000 unit extract of that pollen he is entitled to treatment for at least one year. If his condition is improved one is that much to the good, while if he is no better there is nothing lost. As is known, patients vary tremendously in their sensitiveness and there are undoubtedly some whose skin is almost insensitive. In these persons occasionally pure pollen dropped in the eye will give a reaction, or if blown up the nose it will induce sneezing. As a rule such patients require very large doses, up to 30,000 units or more, and this maximum should be reached before the season opens. These patients should be carefully watched as they may not be able to take such large doses without constitutional reactions.

In this same group will be found patients whose history does not correspond with any known pollen season. Their trouble may begin the end of July or early August, ending in early September or lasting into late October when there is no pollen in the air. If they react to ragweed they may be somewhat improved but not entirely relieved by ragweed injections, while if their skin tests are negative to a strong ragweed extract the treatment is almost certain to be a failure. It will be necessary then to go more carefully into the question of molds, environmental factors, as house dust or animal danders encountered on summer vacation, seasonal fruits and vegetables and infection. It is with this relatively small group that real difficulties in the treatment of hay fever will be encountered.

Treatment

Preseasonal Dosage. The object of treatment is to arrive at the largest dose of extract of the pollens to which the patient is sensitive and exposed, without inducing constitutional or too marked local reactions.

and to do this before the season opens. This dose or a smaller one should be repeated every week or two, as necessary, through the season. When there is a good deal of pollen in the air it is sometimes wise to reduce the dose. The first principle to be grasped is that patients vary tremendously in their sensitiveness and that each has a different optimum dose which must be discovered. With this dose of a properly chosen extract the great majority of patients will have a satisfactory result, although there are a few who apparently cannot build up satisfactory protection because of constitutional reactions (see Chapter 11).

Table 25 gives the average dosage for patients in classes "A," "B," "C," and "D," as determined by the skin test (see p. 195).

TABLE 25

Average Dosage of Pollen Extract Based on Skin Reactions

Dose No.	*Class A* Marked to 10 Units	*Class B* Marked to 100 Units	*Class C* Marked to 1000 Units	*Class D* Moderate to 1000 to 10,000 Units
1	5*	20	50	100
2	10	40	100	300
3	15	80	200	600
4	20	140	350	1000
5	30	200	500	1500
6	50	300	600	2500
7	70	500	800	3500
8	100	700	1200	5000
9	150	1000	1600	6000
10	200	1500	2000	8000
11	300	2000	3000	10,000
12	400	3000	4000	12,000
13	600	4000	6000	16,000
14	800	5000	8000	20,000
15	1000		10,000	

***Dosages in protein nitrogen units per milliliter. Prophylactic therapy: Injections at 4 to 7 day intervals.**

It is important to keep in mind that this is only a rough estimate and does not mean that every patient in class A can take 1000 units as his top dose nor that 1000 units will surely be enough to protect him. This also holds true for the other classes. The majority will fall within the limits of their class, but there will be many exceptions. It is the physician's duty to find out each patient's optimum dose regardless of how he reacts on skin tests. In actual practice this classification is chiefly of value in determining the first few doses, going carefully with those in class A and a little more boldly with those in C and D. After the first few doses the subsequent dosage is modified according to the extent of the local reactions or the occurrence of constitutional upsets. If there is little or no local reaction the doses may be increased more rapidly than the schedule shows and the maximum dose reached may be larger than the classification calls for. If the local reactions are moderate or marked the same dose should be repeated several times or even reduced and subsequent increases made more gradually. The maximum dose may be much below that for the average of the class, but if it is all the patient can tolerate the results are usually satisfactory.

Above all one should avoid inducing constitutional reactions as they are always bothersome and nerve-racking for both doctor and patient and occasionally may be dangerous. A few fatalities have been reported from pollen injections but they are remarkably few if one considers the chances taken by thousands of inexperienced workers. Even if the reaction is mild and apparently no harm has been done, the patient's capacity to receive increasing doses is often limited in some way, and the final dose attained may be much below that which could have been reached if the systemic reaction had been avoided. During the first year of treatment it is better to keep the patient a little underdosed, even if he has mild hay fever, rather than to take the chance of an overdose which may ruin his whole season and upset his confidence. After the first year his capacity can be judged much more accurately and the dosage increased with less danger of a general reaction. After several years of treatment most patients can take much larger doses than at first, but this is not always true as some seem to have a so-called "ceiling" above which they cannot go without a reaction and below which they are perfectly comfortable.

On the average it takes from twelve to fifteen injections to reach a maximum dose and these should be given at four to seven-day intervals. While much has been written about short and intensive treatment with injections every one, two or three days, it has been my experience that if the interval is less than four days the danger of a reaction is greatly increased. Theoretically the period of treatment is decreased from eight or ten weeks to three to reach a maximum dose, which would of course be an advantage, but if reactions intervene the ultimate result will be poor and this advantage completely lost. As a matter of fact it is better to allow three months, which gives some leeway in case of intercurrent illness or some other reason for missing an injection. If this is explained the patient is usually willing to follow the more conservative plan.

During the season injections may be given at one to three-week intervals, depending on the symptoms and local reactions. If the hay fever improves after each injection the dose is all right and may be repeated at five to seven-day intervals if necessary, but if the hay fever is regularly worse after each injection the dose should be decreased and the interval lengthened. Occasionally there are patients who cannot take a full dose when there is much pollen in the air and for these the dose should be decreased during the season. This method is termed "prophylactic treatment" and is the method of choice for most cases.

Co-Seasonal Dosage. If the patient comes in for treatment shortly before the season opens or even after it has begun, some relief may be obtained by giving small doses every day for two or three days and then gradually increasing at two, three and four-day intervals. This is called "phylactic" treatment and the relief obtained is often worth while, but of course the maximum dose can never be reached and the result is rarely as good as with the prophylactic method.

Perennial Dosage. If a patient has done well it is often advisable to repeat the maximum dose every four weeks during the winter to maintain the immunity. This is called "perennial treatment." The advantages claimed for this method are that the results are better, it is more apt to induce permanent immunity and the number of injections is lessened. Figure 16 shows the comparative results obtained over a five-year period with perennial and prophylactic treatment. The satisfactory results with perennial treatment run about 10 per cent higher than with prophylactic, but it must be remembered that it is easier to persuade people who have had a good result to continue through the winter and that these same people are more apt in the long run to attain a "cure." In other words, this group unintentionally is a selected one while the prophylactic cases are the "run of the mill."

The second advantage claimed, that of lessening the number of injections, also needs some explaining. While the doses are given every four weeks through six months in the winter (and the interval must not exceed four weeks because of the danger of inducing a constitutional reaction), when spring comes and a change is made to a fresh extract, which is much more active, the dose must be dropped to 25 to 30 per cent of the old extract and then rapidly built up at two-week intervals to the original dose. This takes three or four extra injections to which must be added any extra weekly injections during the season if the patient is not doing well. If these extra doses are counted only three or four injections at the most are saved. One real advantage to the doctor, if he is treating many patients, is that the load is distributed over the whole year rather than being concentrated into a few months.

There are several distinct disadvantages connected with perennial treatment, the first being that many patients apparently become saturated and develop constitutional reactions from doses they previously tolerated, even when the proper interval is maintained. If this happens several times all treatment should be discontinued until spring and then resumed prophylactically at weekly intervals, beginning with the smallest dose. Another disadvantage is that many patients will fail to come in for a month or two, making it necessary to cut the dose to half or less and then build up again at two-week intervals. Perennial treatment should not be used with patients who have had a poor result, for it is evident that their mixture or dosage is not correct and it is advisable to wait and start again in the spring after retesting. It is my custom to explain the advantages and disadvantages of perennial treatment to my patients and let them choose which they prefer. I have no accurate figures, but I believe that the end results in the two groups are about equal.

Combination Extracts. The problem would be much simpler if a person were only sensitive to a single pollen, but of course this is not often the case. The ideal method would be to give separate injections of each pollen that is needed, but that is impracticable. Hay fever is an inconvenience rather than a dangerous or fatal disease and one must avoid making the treatment a greater nuisance than the original complaint. The simplest method is to determine the pollens to which a patient is sensitive and exposed, as well as his degree of sensitiveness to each, and then combine them in one special, individual mixture so that he will require only one injection each visit. This requires some skill and experience, but in the long run is worth the trouble and usually works well.

Method of Preparation. In the first place, the more sensitive a person is to a particular pollen the smaller is the dose of extract required for protection. The dose will also vary according to the amount of pollen encountered, heavier doses being needed for heavier pollen exposure. Let me illustrate with the simplest form of a combination extract. A patient suffers from hay fever from mid-May until the end of July and gives marked reactions to 100 unit strengths of both timothy and plantain, with little or no reaction to sorrel. The pollen content of the air is about equal for both plantain and grass, hence he should have a mixture of equal parts of both extracts. Use 6 ml. each of a 5000 unit extract of timothy and of plantain and mix them in one bottle. One milliliter of this will obviously contain 2500 units of timothy and 2500 units of plantain. Mark this bottle #3 and mix 1.5 ml. from it with 6 cc. of diluting fluid (making a 1:5 dilution) and mark this bottle #2. One milliliter from this will equal 1000 units of the mixture. Take 1 ml. from bottle #2 and add it to 4 ml. of diluting fluid and mark this bottle #1. It will contain 200 units of the mixture per 1 ml. Start injections with 0.1 ml. from bottle #1 (or 20 units of the mixture) and continue according to the schedule for a class B patient. There will be plenty of extract in each bottle for the doses required from that bottle (a surplus in #1 and #2) with enough in #3 to last through the season. While the total dose of 1 ml. of bottle #3 is 5000 units of the combination (the theoretical top dose for a class B patient), it is only 2500 units of each pollen, which may be sufficient to protect him, but if the local reactions are not too severe it may be advisable to make up a 10,000 unit bottle and continue with this. Furthermore, 0.5 ml. of 10,000 units will probably produce less local reaction and be less uncomfortable than 1 ml. of 5000 units, which is an advantage.

If the patient does well during the end of May and the first part of June (the height of the plantain season) but has trouble during the end of June and in July, it is evident that his plantain dose is all right but the dose of timothy pollen should be increased, and another year the mixture may be made with one part plantain and two parts timothy.

If the pollen content of the air is heavier for one pollen than for another, naturally more of that extract is put into the mixture. Patients whose hay fever runs through the summer (with symptoms abating for several weeks the end of July and early August) and who react to both timothy and ragweed are often encountered. They will evidently need more ragweed than timothy and the usual proportion is one part timothy to two, three or even four parts of ragweed.

If the patient is more sensitive to one pollen than another, less of that one pollen is required in the mixture. If, in the first instance cited, the patient gave a marked reaction to 10 units of plantain and a moderate or marked reaction to 1000 units of timothy, one part of plantain and four parts of timothy would probably be used, varying the proportion in later years as necessary.

Naturally, too many pollen extracts cannot be put into one mixture as that would reduce the dose of each. With the trees, six or eight may be included if necessary, as relatively small doses of each are required to give protection. I have often found 200 to 300 units of each to be sufficient. The dose necessary to protect against plantain and timothy is higher than for the trees on the average. To protect against ragweed, with its pollen content in the air very heavy, a very concentrated extract is usually needed which consequently cannot be diluted with other pollens.

Mixtures Commonly Used. Making up mixtures of pollens in advance saves figuring and bother when the patients come in for injections, and with a little care and experience the results justify the procedure. As a matter of fact, one will find that six or eight mixtures suffice for ordinary use. This list will comprise, for the Early hay fever, equal parts of timothy, plantain and sorrel, or one-half timothy and the other half plantain and sorrel. For the Early and Late hay fever, one part timothy and two or three parts ragweed, or one-half timothy and plantain and one-half ragweed. For the Late hay fever one-half or two-thirds ragweed and the rest a combination of the other fall weeds, amaranth, artemisia, chenopod, cocklebur and Iva, depending on how the patient reacts to some or all. As these latter occur in much lower concentration on the East Coast than does ragweed pollen, it will not require nearly so large a dose to give protection against them. The combinations for the tree mixtures may be much more varied, but in view of the small individual doses which may be necessary they can often be combined with Early and Late mixtures without too great dilution. The ragweed extract is always made up of half high ragweed pollen (Ambrosia trifida) and half low ragweed pollen (Ambrosia elatior), while timothy pollen alone is used to protect against grass sensitization rather than a mixture of different grasses. The results are just as good and it saves considerable effort. Before making up a final mixture it is well to give two or three doses of the pollens separately and judge by the local reactions the proper proportions for the mixture (Vander Veer[16]).

I do not believe it is good practice as a general rule to add other extracts, as animal danders, orris, and the like, to pollen mixtures, except possibly house dust and then only if the vasomotor symptoms are present summer and winter and perennial treatment is planned.

Constitutional Reactions. These are fully discussed in another chapter (p. 210) and I shall mention here only the essential points. The chief causes of a constitutional reaction are the injection of a larger dose than the patient can tolerate, too large an increase in dose or the injection of the extract directly into a vein instead of into the subcutaneous tissue. The last can be guarded against by withdrawing the plunger of the syringe slightly before the dose is injected; if a little blood is drawn into the syringe it means that the needle is in a vein and must be withdrawn a little or inserted a little deeper before the injection is made. Avoiding the other two causes is merely a matter of judgment and experience, but no matter how careful a physician may be a reaction will occur occasionally. On the average about 10 per cent of the patients will have a reaction at some time and a reaction will occur in about one-half per cent of all injections. If the average exceeds this it means there is something wrong with the technic or with the judgment of the physician.

Constitutional reactions are the one great drawback to the injection treatment and should be guarded against in every possible way. They are always disagreeable, sometimes dangerous and very rarely have proved fatal. They also upset the patient's tolerance and often result in his not being able to take adequate doses to protect him against the hay fever. One should never do any testing nor give any injection, no matter how simple, without having at hand a tourniquet and a bottle of epinephrine (1:1000). The first signs of a constitutional reaction are itching of the palms of the hands or of the body, sneezing, cough and redness of the face. The sooner this occurs after an injection the more violent the reaction is apt to be. At the first sign of trouble a tourniquet should be applied above the injection site and a dose of epinephrine given above the tourniquet or in the other arm. If the reaction has been delayed and seems mild a dose of 0.2 to 0.3 ml. may be sufficient and may be repeated in a few minutes if necessary. If the reaction is sudden and severe 0.6 to 1 ml. should be given at once and well massaged into the tissues, and the dose should be repeated in a few minutes if there is no marked improvement. Blanching of the tissues at the site of the epinephrine injection is usually a sign that the reaction is under control and the tourniquet may be gradually released. In reactions which threaten to prove fatal epinephrine may be given intravenously in 0.3 to 1 ml. doses. If too much epinephrine is given or if it is injected into a vein by mistake, the patient will have a mild or severe headache with blanching of the nose and face, palpitation and tremor. This usually clears rapidly without too much discomfort. Even in patients with high blood pressure I have never seen any bad effects from the epinephrine.

Rarely the constitutional reaction may take the form of abdominal or uterine cramps which are particularly dangerous in pregnancy, although this does not often result in a miscarriage. In this abdominal type of reaction a small dose of epinephrine followed by codeine or morphine often is more effective than epinephrine alone. If one is treating a pregnant patient for hay fever the doses should be kept at a safe miminum and discontinued as soon as the season is over. In other words, perennial treatment is not advised. Whenever a constitutional reaction does occur the next dose should be cut to one-half or two-thirds and given after an interval of a week. Subsequent increases should be very gradual.

Age to Begin Treatment. In general as soon as definite clinical hay fever has been diagnosed treatment should be instituted. If the patient is under six years of age one may temporize for a time by sending him to pollen-free areas in the summer, but after that age these children take treatment just as well as adults. The earlier the treatment is begun and the more faithfully it is kept up the more chance there is of a permanent immunity developing in the course of time. It is foolish and dangerous to allow hay fever to continue year after year on the theory that the patient will eventually outgrow it. Very few patients do so and many may have more serious trouble, such as frequent colds, sinus infection and seasonal asthma.

Commercial Extracts. While it is, of course, a great advantage to work with extracts prepared in one's own laboratory, this is impracticable for the general practitioner because of the expense involved. Those who are especially interested in allergy will usually be connected with a hospital or clinic and have access to the extracts prepared there. The doctor who treats only an occasional case must depend on the extracts manufactured by the commercial drug houses, and on the whole these are quite satisfactory. Most of them call for testing by the scratch method, instead of the intradermal, which is a little less accurate (but less dangerous). These extracts are usually put up with glycerin to prevent deterioration. The principle of increase in dosage is the same as has been described here and is facilitated by using two or three bottles of varying strengths. Many of them are standardized according to the pollen protein nitrogen unit system, but when other systems are used the same rate of increase in doses is observed. A fair number of standard combination extracts are obtainable and special combinations can be prepared on order. Some of the houses publish pollen charts for different localities and descriptive literature is sent out with all the preparations.

It is not to be expected that as good results can be obtained with standard commercial extracts as with special individual combinations, but for the average case they may work very well and are of course less expensive.

Self Injections. In order to further simplify the treatment I have for many years allowed some of my patients, who requested it, to give their own injections. Since the introduction of insulin and epinephrine thousands of people have been giving themselves hypodermic injections and it is not difficult to teach them asepsis and the graduation of doses. Patients are given a very simple direction sheet with the schedule of injections clearly outlined. The principle of increasing dosage is explained, as well as the dangers and the treatment of a constitutional reaction (an ampoule of epinephrine is enclosed with every extract sent out) and the first two or three injections are supervised. The percentage of constitutional reactions is no greater than when injections are given by a physician. I have almost never seen an infection resulting from an injection, and as most patients are intensely interested in their own welfare they are much more regular in their treatment than if they must go to a doctor every week. It is also an advantage for an asthmatic patient to know how to administer a dose of epinephrine to himself in case of an attack in the middle of the night when a doctor may not be available. Of course, in the case of very sensitive patients, particularly those who have had constitutional reactions in the past, I insist on their taking the injections from a doctor. There are a great many people who prefer to do this anyway.

Adjuncts to Injections. Window ventilators and air conditioning help a great deal to reduce pollen contact. Of the former there are many successful models on the market costing from sixty to one hundred dollars. They filter the pollen from the air, but of course do not cool the room, and on hot nights patients are uncomfortable. Air conditioning may cost from several hundred to a thousand dollars for a room, but this, of course, includes cooling and dehumidifying the air as well as filtering out the pollen and dirt. If neither of these is available the patient may sleep in a room with the windows closed, the ventilation coming from an adjoining room. This keeps out much of the pollen. Often the nose drains better if the patient sleeps propped up on several pillows, but be sure he is not feather-sensitive. These measures are rarely necessary for simple hay fever, but for asthma they may be very helpful. Every well-equipped hospital should have at least one or two air-conditioned rooms reserved during the season for severe pollen asthmatics.

Medication. Capsules of ephedrine and amytal are of more help in asthma than in hay fever but they may be used. Injections of epinephrine are of little use. Ephedrine is used locally in every possible combination, aqueous solution, in oil, in jelly, and so on. The immediate effect is very good but if used to excess (which is a great temptation) the mucous membrane soon becomes soggy and the nasal congestion may continue the discomfort long after the pollen has disappeared from the air.

Among the newer preparations which give promise of being of help in the treatment of allergic conditions, particularly vasomotor rhinitis and urticaria, are pyribenzamine (n′-pyridal-n′-benzyl-n′-di-methyl ethylene diamine mono-hydrochloride) (Ciba) and benadryl (b-di-methyl amino-ethyl-benzhydryl-ether-hydrochloride) (Parke Davis). Their therapeutic action is based on the assumption that the drug neutralizes the histamine-like substance supposedly released in the shock tissue during an attack, thereby affording symptomatic relief.[18]

While it is too soon to give an adequate appraisal of their worth, reports thus far indicate that they may have value in the temporary relief of vasomotor rhinitis and hay fever, possibly in urticaria or migraine, but have been disappointing when tried in bronchial asthma and eczema.

A large percentage of the patients in whom they have been tried show some side effects which are seldom serious. The most frequent of these are drowsiness and occasional nausea. No serious reactions to their use have been reported as yet. The usual adult dose of both of these drugs is 50 mg. every three to four hours, as necessary.

Anthallan (3′di-(n-butyl) amino-methyl-1,4,5,6-trihydroxy-benzo (1,2,-c) furan -1′(3′)- one) has not yet received adequate trial but Ghiselin[19] reported improvement in eleven cases. Literature on the pharmacologic and toxicologic action has not yet been made available.

An excellent eye drop prescription is:

	gm. or ml.
Cocaine hydrochloride	0.1
Boric acid	1.0
Epinephrine hydrochloride (1:1000)	8.0
Rose water in sufficient quantity to make	32.0

Mix and label: Eye drops. Put one or two drops in each eye when inflamed.

This is really very helpful not only for the itching and congestion of the eyes but also for the itching of the palate. It too should be used sparingly as the cocaine may dilate the pupil and disturb the vision for several hours.

Atropine 1/200 grain (by mouth) will lessen nasal discharge and may clear the nose, but works better when combined with phenacetin and caffeine. A good prescription is

	gm. or ml.
Atropine sulfate	0.002
Caffeine citrate	0.5
Phenacetin	2.0

Mix and make 15 capsules. Label: one capsule every 3 or 4 hours.

Ascorbic acid, potassium chloride and hydrochloric acid medication are useless while ionization and cauterization of the nasal mucous membrane are not only worthless but may have serious after-effects.

Diet. A few people are sensitive to seasonal fruits and vegetables such as melons, peaches, berries, asparagus, tomatoes, corn and celery. These may be excluded from the diet if suspected, sometimes with benefit, but it is useless to cut out all proteins (which is the usual procedure) as meat, fish and eggs, which do not cause trouble in the winter.

Resorts. Before the war there was an annual exodus of hundreds of thousands of people who did not wish to take injections for hay fever to various places which were, or were supposed to be, pollen-free. During the war years, of course, travel was greatly restricted even in our own country and Europe has been out of the question. In general the pollen content of the air is low in the midst of large forests and along the sea coast where the prevailing winds are from the ocean. In the eastern section of this country the best known hay fever resorts are in northern Maine, central Adirondacks, and Fire Island Beach, Long Island, New York, particularly Montauk Point. The Catskills and the White Mountains are less satisfactory. Canada, Nova Scotia and New Brunswick and the Gaspe peninsula may furnish relief, while the Upper Michigan peninsula and northern Wisconsin are all right if one goes far enough in the woods. As pollen will travel hundreds of miles on a strong wind, any of these places may be invaded at times. For a list of specific towns and hotels it is well to consult a travel bureau, bearing in mind the general region where one might hope to be free.

Results

With proper care and experience 80 per cent of the treated patients should have at least 80 per cent relief from their hay fever and nearly half of these will be completely free. Fifteen per cent will have slight or moderate relief and 5 per cent will have no relief at all. These figures are gathered from the reports of many physicians over the country and cover many years of experience, so they may be considered reliable. If the results fall below this the physician is not up to standard. Naturally the more experience the physician has and the more care he takes the better his results should be.

In addition to the relief of the hay fever there are several side results which should be taken into consideration. Successfully treated patients are less apt to develop winter colds and sinus infection and rarely develop seasonal asthma. Thirty per cent of the untreated cases eventually do develop pollen asthma, which often runs into the perennial type, and as this may be very difficult to cure it is imperative that the hay fever be thoroughly treated before this occurs.

One of the first questions a patient may ask when he comes for treatment is as to the chance of a permanent cure. To this one can only say that some people do outgrow hay fever after a varying length of time, but that many more continue with it practically all their lives. There is no question but that treatment is more helpful toward effecting a cure than a policy of letting nature take its course, but it is impossible to tell whether any individual patient will fall into the cured group. Another unfortunate fact is that one can rarely tell when a patient is cured, as he may have a positive skin test (often diminished, it is true) for many years after the eyes and nose have become clinically insensitive. My own procedure is to advise a patient who has gone for several years without hay fever, even when he has taken only one injection a month through the season, to take a chance and stop treatment. Some patients will refuse to take such advice while others will stop treatment and often remain two or three years or more without symptoms. Some patients never have any more trouble while others have a gradual return of the hay fever. These patients must start in again with injections (Vander Veer and Clarke[17]).

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11. Allergic Rhinitis: Seasonal—Continued

SPECIAL FEATURES OF RAGWEED HAY FEVER

SELIAN HEBALD

In the literature on the treatment of hay fever, the clinical results from specific therapy have been quite satisfactory in the large majority of cases treated; patients took their dosage well and results varied from excellent to good to fair. However, in any large group of cases observed, there was always a goodly number in whom trouble was encountered.

Constitutional Reactions

Systemic reactions resulting from injections of pollen extract constitute one of the chief difficulties in the treatment of hay fever. While some of these may be attributed to errors in technic or in judgment as to dosage, even the most experienced physician cannot avoid them entirely. In many patients these general reactions occur at low dosage, and in addition to the general reactions, a poor clinical result is obtained.

Studies which throw some light on these difficulties have been made on the ragweed-sensitive cases because such patients usually have more severe symptoms than those with the earlier types of seasonal hay fever, they are more difficult to control, and many more cases are available for study.

In the course of a study[1] of fresh and modified ragweed pollen extracts, one group of patients was tested and treated with extract heated to 70° C. for one hour. Clinically ragweed-sensitive patients were tested intradermally with the regular alkaline-saline extract and with the heated extract in strengths of 10, 100 and sometimes 1000 units of protein nitrogen per milliliter. It was noted that some patients were equally sensitive to identical strengths of both the heated and unheated extract, while others were very much less sensitive to the heated extract. In the group of patients treated for two seasons with heated extract, clinical results on the whole were poor and many general or constitutional reactions were obtained. It was also noted that the general reactions occurred much more often in those patients who on direct skin test were as sensitive to the heated as to the regular extract. The significance of these observations, at first not understood, can now be explained.

Antigenic Fractions of Ragweed Extract. Chemical fractionation of ragweed extract was carried out and the original publications from the

Allergy Department of Roosevelt Hospital by Stull et al.[2, 3] explain in detail the methods used in obtaining three antigenic fractions. In brief the procedure was as follows:

One hundred grams of anhydrous ethyl ether defatted low ragweed (Ambrosia elatior) pollen was extracted with 1000 ml. of distilled water at 7° C. for twenty-four hours, and the pollen residue was separated. The *p*H of the filtrate, which was 5.9, was adjusted to *p*H4 by the addition of tenth-normal hydrochloric acid. Gradually a precipitate, later designated Fraction 3, was formed and was removed by centrifugalization. The supernatant fluid was then brought up to 50 per cent of saturation with ammonium sulfate. This produced another precipitate which was designated Fraction 1. The supernatant fluid was filtered and ammonium sulfate was added to full saturation. Another precipitate now formed and this was designated Fraction 2. Fractions 1 and 2 were reprecipitated many times for purification and finally were dialyzed against running water and then against distilled water until free from sulfate.

In a typical extract of low ragweed pollen, Fraction 1 and Fraction 3 each made up approximately one fourth of the total protein nitrogen, while the balance or 50 per cent was Fraction 2. The three fractions, on a protein nitrogen basis (1 unit = 0.00001 mg. protein nitrogen) were compared by various chemical and biologic tests. Similar fractions have also been separated from giant ragweed (Ambrosia trifida).

Fraction 1 is a substance typical of protein both in physical and chemical properties and in nitrogen content. It has all the qualities necessary to fulfill the requirements of an active substance in ragweed pollen because it gives positive skin tests directly in all clinically sensitive hay fever patients and in sites made with serums of such patients (passive transfer). It neutralizes or reduces the activity of sensitizing serums against test with whole ragweed extract. Also it shows antigenic specificity in guinea pigs and is thermolabile; heating at 70° C. for one hour inactivates it. It contains about 12 per cent nitrogen, but does not contain carbohydrate. It resembles vegetable albumin.

Fraction 2 in certain lots contained as high as 12 per cent nitrogen. It has antigenic properties as shown by reactions in ragweed-sensitive man both directly and on passive transfer and in artificially sensitized guinea pigs. It is thermostabile and is similar to vegetable proteoses.

Fraction 3 gives positive skin tests in certain ragweed-sensitive patients and in skin sites passively sensitized with certain ragweed-sensitive serums. It resembles plant glutelins. Little work has thus far been done with this fraction.

The three fractions show marked differences in their capacity to neutralize ragweed-sensitive serums. Fractions 2 and 3 both require much higher concentrations for serum neutralization than Fraction 1. Fraction 1 is by far the most active fraction.

Large numbers of ragweed-sensitive patients were tested with the three fractions in strengths of 1, 10, 100 and 1000 units of protein nitrogen per milliliter. All were sensitive to Fraction 1. Some were equally sensitive to Fraction 2, while others gave little or no reaction to tests with Fraction 2 in the dilutions ordinarily used for intracutaneous tests. There were also a few who were more sensitive to Fraction 2 than to Fraction 1.

Clinical and serological studies[4] with Fractions 1 and 2 and whole extract have yielded results which have a practical bearing on the management of "problem cases" and throw light on the reason for constitutional or general reactions occurring even with low doses of regular extract. I shall review some of the more important of these observations.

Two hundred and twenty-one ragweed hay fever patients were tested intracutaneously with suitable dilutions (containing 1, 10 and 100 protein nitrogen units per milliliter) of each of the Fractions 1 and 2. A large number of these patients were "problem cases" and had had numerous constitutional reactions in previous years of therapy with regular extract. Patients who took large doses of regular extract well were also tested and the group included new patients as they came to the clinic for treatment after they had received injections of regular extract for one season. In all about one-half the patients in the group had had one or more constitutional reactions. This, of course, was very much higher than the incidence in the clinic as a whole because of the deliberate inclusion of the many difficult cases.

TABLE 26

REACTIVITY OF RAGWEED-SENSITIVE PATIENTS TO FRACTIONS 1 AND 2 IN RELATION TO INCIDENCE OF CONSTITUTIONAL REACTIONS

Intracutaneous Tests	*Total Cases*	*Cases Having Constitutional Reactions*	*Percentage of Cases Having Constitutional Reactions*
F I > F 2	93	13	14
F I = F 2	108	81	75
F 2 > F I	20	16	80

Sherman & Hebald: Am. J. M. Sc., *203*:383, 1942.

Table 26 shows the incidence of constitutional reactions in patients classified on the basis of the relative activity of the skin reactions to the two fractions. Ninety-three gave larger skin reactions to Fraction 1 than to Fraction 2. Of these, thirteen patients (14 per cent) had one or more constitutional reactions during treatment, many of them minor. One hundred and eight patients had skin reactions of equal size to the two fractions. Of these, eighty-one (75 per cent) had constitutional reactions. There were only twenty patients who showed greater skin reactions to Fraction 2 than to Fraction 1, but of these, sixteen (80 per cent) had general reactions. Since the occurrence of general reactions in the last two groups was more than five times that in the first group, it seemed clear that these skin tests gave an index of the probability of a constitutional reaction.

It appeared logical that the actual degree of reaction to Fraction 2 was more important than the relative size of reactions to the two fractions. A comparison of the value of skin tests was then made with regular ragweed extracts and Fraction 2 as a basis for predicting constitutional reactions. A group of ninety-five patients was classified A, B, and C by the method of Cooke (p. 198)[5, 6, 9] according to whether it required dilutions containing 10, 100 or 1000 protein nitrogen units per milliliter of the regular ragweed extract to produce a marked intracutaneous reaction with pseudopods. The same patients were then reclassified on a similar basis, using (for the tests) solutions of Fraction 2 containing the same amounts of protein nitrogen.

TABLE 27

INCIDENCE OF CONSTITUTIONAL REACTIONS IN RAGWEED-SENSITIVE PATIENTS CLASSIFIED BY SKIN REACTION TO WHOLE RAGWEED EXTRACT AND TO FRACTION 2

Class	*Total Cases*	*Cases Having Constitutional Reactions*	*Percentage of Cases Having Constitutional Reactions*
	Classified by Test with whole Extract		
A	15	8	53
B	41	25	61
C	39	17	44
	Classified by Test with Fraction 2		
A	9	8	89
B	25	21	84
C	61	21	34

Sherman & Hebald: Am. J. M. Sc., *203*:383, 1942.

Table 27 shows the relative incidence of constitutional reactions in the three classes when the classification was based on tests with regular extract and when it was based on tests with Fraction 2. It was clear that the test with regular extract was no criterion of the probability of general reactions. The moderately sensitive class (B) had a higher incidence of reactions than the exquisitely sensitive class (A) and the incidence in the least sensitive class (C) was only slightly lower. Reclassification on the basis of the test with Fraction 2 gave more information, classes A and B having an incidence of reactions two and one-half times that of class C.

Table 28 illustrates a classification in which the groups are more nearly equal as to number of patients. Here 214 patients, including some not considered in Table 27, are classified on the basis of the degree of reaction to skin test with a solution of Fraction 2 containing 100 protein nitrogen units per milliliter. Seventy-nine patients gave a slight reaction or no reaction at all; of these, ten (13 per cent) had constitutional reactions. Sixty-four patients gave a moderate reaction, without pseudopods; of these, thirty-four (53 per cent) had general reactions during treatment. Of the seventy-one patients who gave a marked skin reaction, sixty-two (87 per cent) had constitutional reactions. In other words, the group most sensitive to the 100 unit solution of Fraction 2 had seven times as high an incidence of constitutional reactions as the least sensitive, while the group with moderate reactions was midway between. Although these figures tell the story fairly well, they do not reveal one important aspect. Many of the patients in the less sensitive group who were listed as having constitutional reactions had one or two reactions, often following what in retrospect was seen to be a too sharp increase in dosage, but subsequently went on and tolerated much larger amounts of extract without trouble. On the other hand, practically all of the patients who received a dosage that was low, but above which they could rarely be raised without inducing a constitutional reaction, fell into the group most sensitive to Fraction 2.

TABLE 28

SKIN REACTION TO FRACTION 2 (100 UNITS PER ML.) IN RELATION TO INCIDENCE OF CONSTITUTIONAL REACTIONS

Intracutaneous Test	*Total Cases*	*Cases Having Constitutional Reactions*	*Percentage of Cases Having Constitutional Reactions*
Slight-negative	79	10	13
Moderate	64	34	53
Marked	71	62	87

Sherman and Hebald: Am. J. M. Sc., *203*:383, 1942.

Similar information was obtained when the reaction to the two fractions was tested by the method of passive transfer. In a series of eighty-nine patients, the group whose serums sensitized normal skin to Fraction 2 gave an incidence of constitutional reactions almost three times that of the group whose serums did not react with this fraction in the dilution used. Results obtained by this method gave no information not obtainable by direct skin test.

No matter how the cases were classified, there were always a certain number of exceptions. This could have been predicted from the serologic studies by Sherman[7] which showed that some patients (about 10 per cent) do develop a blocking antibody for Fraction 2 in the early stages of treatment while a few others develop blocking antibody for Fraction 1 either very slowly or not at all. No attempt was made to determine the blocking antibodies in the serums of most patients. However, serum was taken after treatment from six patients who were definitely sensitive to Fraction 2, but had received large doses of regular extract without constitutional reactions. Four of the six serums inactivated Fraction 2, indicating that the behavior of these patients was due to the fact that blocking antibody for Fraction 2 was present in their serums. Because of the technical limitations in the method used, it was not possible to exclude the presence of small amounts of blocking antibody for Fraction 2 in the other two serums. On the whole, the results strongly suggested that the two fractions were specific antigens and that the blocking antibody, which is also specific, was an important factor in acquired tolerance for injections of antigen. For details concerning the blocking antibody,[8] see Chapter 3.

More important from a practical viewpoint, however, was the fact that intracutaneous tests with Fraction 2 seemed to offer valuable information for judging the probability of constitutional reactions. A good basis for planning the range of doses of pollen extract for a ragweed hay fever patient is afforded by skin tests with whole extract and each fraction in dilutions of 10 and 100 protein nitrogen units per milliliter. The tests with the whole extract (and Fraction 1) give an indication of the safe initial doses while the test with Fraction 2 indicates the probabilities of general reactions with increasing dosage.[4]

Treatment with Antigenic Fractions. There were some patients who gave strong reactions to Fraction 2 and were unable to take large doses of regular extract who had good clinical results when treated with small doses. Yet there were many more for whom small doses of regular extract did not give adequate protection. These were the particular "problem cases" and a number of them were treated with extracts of the fractions.

One group was treated with Fraction 1 only. The patients of this group included both good and poor reactors to Fraction 2. All were sensitive to Fraction 1. The clinical results were good, better than 75 per cent relief, particularly in those patients who were poor reactors to Fraction 2. In those patients who were highly sensitive to Fraction 2, the results were not so good. These patients apparently needed some Fraction 2 for their clinical protection. High dosage with Fraction 1 was usually reached and constitutional reactions were few.

A second group was treated with Fraction 2 only. Here again the patients fell into two classes of highly sensitive and moderately or slightly sensitive to Fraction 2. All were sensitive to Fraction 1. The clinical results in this group were poor and many constitutional reactions were obtained in those patients who were highly sensitive to Fraction 2. The results of treatment with Fraction 2 seemed to be about the same as those obtained by treatment with the heated whole extract previously described when Fraction 1 being thermolabile had been destroyed in the heating. The omission of Fraction 1 in the therapy of this group apparently made an important difference in the clinical results.

A third group of patients was treated with both Fraction 1 and Fraction 2. Again the patients could be divided according to their greater or lesser sensitivity to Fraction 2. All patients were sensitive to Fraction 1. Dosage with Fraction 1 could be stepped up normally in both groups with few exceptions—often to 5000 units of protein nitrogen or more. But Fraction 2 could not be increased to large amounts in those patients who on skin test were highly sensitive to this fraction, without constitutional reactions being obtained. The general clinical results in this group were good.

The fourth and last group of patients was treated with regular extract supplemented by Fraction 1. In this group all the patients previously had had constitutional reactions; all had done poorly in previous years of therapy on regular extract; all were able to take only small amounts of regular extract without developing general reactions; and all the patients were highly sensitive to Fraction 2. In treating this group, Fraction 1 extract was added to the "ceiling" dosage of regular extract. It was very interesting to note that patients who could not take more than 500 or 1000 protein nitrogen units of regular extract were able to take in addition 2000 or 3000 protein nitrogen units or more of Fraction 1 without developing general reactions. A large majority of patients in this group showed much better clinical results under this treatment than was afforded in previous years with regular extract of ragweed alone in the necessarily low doses permitted because of their sensitivity to Fraction 2.

These points are well illustrated in the case history of JEC, a woman aged fifty-two, who had had typical ragweed hay fever for fourteen years. She was treated for one season about ten years before with no relief. As she put it, each injection made her sick.

Direct skin testing with extracts of the three fractions and regular extract of ragweed each (100 protein nitrogen units per milliliter) showed the following results:

Fraction 1	marked or	++++
Fraction 2	marked or	++++
Fraction 3	slight or	+
Regular Extract	moderate or	+++

On July 8, 1941, an injection of whole ragweed extract R41, 2000 units, produced a constitutional reaction in five minutes, with symptoms of asthma, cough and flushing. Epinephrine (1:1000) 0.5 ml. was given with quick relief. Her next treatment two weeks later was 700 units of ragweed extract 41, and with slow increases at weekly intervals she was given 1250 units on August 26, 1941. Another general reaction occurred in ten minutes with symptoms of chest tightness, cough and hay fever. Epinephrine (1:1000) 0.5 ml. was given with relief in a few minutes. At the next visit she received 500 units of ragweed extract and slow increases were again attempted. The clinical result for 1941 was poor.

Under perennial therapy, with injections every three weeks, another general reaction occurred when she received 1000 units of ragweed extract on January 13, 1942. The dose was reduced to 300 units and slowly increased to 800 units. She was kept at this level for the 1942 season. The clinical result for 1942 was again poor.

Continuing with perennial therapy at the level of 800 units of whole extract for each injection, Fraction 1 extract now was added, starting with a dose of 3 units and proceeding up. Top dose for the 1943 season was 800 units of whole extract plus 2500 units of Fraction 1. The patient had a good season, stating that she was 85 per cent improved, and no constitutional reactions occurred.

Proceeding through the 1944 season, a top level of 7000 units of Fraction 1 and 1500 units of regular extract was reached on September 5, 1944. The patient had a perfect clinical result, with no hay fever at all for the 1944 season, and no constitutional reactions occurred.

It will be remembered that Fraction 1, the most active fraction, constitutes but 25 per cent of the protein nitrogen in the whole extract while Fraction 2 constitutes 50 per cent. With a top dose of 1500 units of whole extract, this patient received only 375 units of Fraction 1. It was felt that this amount of Fraction 1 was inadequate for clinical protection in this case. The dose of whole extract could not be sufficiently increased because of the marked sensitivity to Fraction 2. In this patient the top level of Fraction 2 tolerated was 750 units. It seemed rather clear that the added dose of Fraction 1 aided materially in the clinical protection for the hay fever seasons of 1943 and 1944.

In summary it may be said that: An analysis of results of treatment in all groups classified as to degree of sensitivity appears to give evidence that Fraction 2 is the great offender in causing constitutional reactions in ragweed-sensitive patients. It is important in causing hay fever in those patients sensitive to it.

Fraction 2 is a thermostabile proteose-like protein precipitated from saturated ammonium sulfate solutions. It is a poor antigen. Marked reactions on skin test with Fraction 2 (100 protein nitrogen units per milliliter) indicate the probability of constitutional reactions with increasing dosage of ragweed extract.

The addition of Fraction 1 to the necessarily small doses of regular extract that can be safely tolerated is indicated in the treatment of these "problem cases" that are highly sensitive to Fraction 2.

Practical Methods of Preparation. Since the special preparations of Fractions 1 and 2 are not yet available to anyone desirous of carrying out the work outlined in this chapter, following are two simple procedures for securing a testing extract of Fraction 2 and for changing the relative proportion of Fractions 1 and 2 in solutions for therapeutic use.

Fraction 2 for Testing Extracts. In extracts standardized on a protein nitrogen basis (phosphotungstic acid precipitate) approximately 50 per cent of the total protein represents Fraction 2. Still unpublished work in collaboration with Stull has shown that a practically accurate and useful testing solution of Fraction 2 may be made by heating the regular low ragweed pollen extract at 70°-100° C. for one hour. A 2000 unit per milliliter dilution thus heated is the equivalent of 1000 unit dilution of Fraction 2 which is then diluted for testing to 100 units and 10 units per milliliter.

Testing with these strengths affords a good index of the probability of constitutional reactions from Fraction 2 in the regular extract. A marked reaction to the 10 unit dilution, occasionally obtained, and one to the 100 unit dilution will classify a large proportion of the so-called problem cases of ragweed pollen hay fever.

Reducing Fraction 2 for Therapeutic Extracts. A second practical suggestion is made for those whose laboratory facilities permit a modification of regular low ragweed extract. The problem is to alter the relative proportions of Fraction 1 (average 25 per cent) and Fraction 2 (average 50 per cent) in regular alkaline-saline extract of defatted low ragweed pollen without undertaking the elaborate preparation of pure fractions. This may be done as follows:

Low ragweed extract, without phenol, is brought to *p*H4 by the addition of dilute hydrochloric acid. After standing at 7° C. for about fifteen hours Fraction 3 precipitates and the supernatant is filtered and brought to 50 per cent saturation with ammonium sulfate. The resulting precipitate is crude Fraction 1.

After fifteen hours at 7° C., the bulk of the supernatant is siphoned off and the remaining mixture is filtered through Whatman's #4 paper. The precipitated Fraction 1 is removed from the filter paper and redissolved in distilled water and, after water-insoluble material has been filtered off, the protein is reprecipitated at *p*H4 with 50 per cent saturation of ammonium sulfate. This procedure is repeated a third time. The precipitate is then dissolved in water, dialyzed against distilled water until free of sulfate and filtered through Whatman's #5 paper. After the addition of 0.5 per cent NaCl and 0.3 per cent $NaHCO_3$, it is Seitz-filtered and tested for sterility. It is then standardized for protein nitrogen of Fraction 1 and 2. The protein of such solutions is now about

90 per cent Fraction 1 and 10 per cent Fraction 2 instead of the original 25 and 50 per cent respectively of Fractions 1 and 2. Final solutions containing a total of 100,000 protein nitrogen units may be obtained.

Since Fraction 1 is unstable, it must be refrigerated throughout the above procedure. 50 per cent glycerine is added to afford additional stability. Upon proper dilution the pollen protein is ready for therapeutic injections.

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12. Allergic Rhinitis: Perennial (Vasomotor Rhinitis—Hyperplastic Rhinitis)

W. C. SPAIN

Disorders of the nose are of common occurrence, due largely to its important function of cleaning and conditioning the inspired air. Located at the entrance of the respiratory tract, it is subjected to the assaults and injuries produced by all manner of disturbing factors such as extremes of heat and of cold, of moisture and of dryness; gases, fumes and chemicals; atmospheric contaminants both inorganic, as soot, dusts of coal and of stone, and organic, as house dusts, powders, animal emanations, pollens, mold spores and bacteria. With considerable success, all of these varieties of foreign substances are combatted by the ciliated moist surfaces of the nasal mucosa, although often at the expense of irritation, inflammation and even severe infection of the involved tissues.

In addition to these general deleterious effects, there may appear in the occasional person a more peculiar, a more uncommon reaction to many of the organic types of foreign substances, a form of irritation wherein there develops a specific sensitization not only in the tissues of the upper respiratory tract but systemically. It is with the occurrence of such nasal allergy that this chapter is concerned.

Many nasal ailments of diverse origin may be classed as cases of rhinitis or coryza. Their causes may be physical, from heat or cold; chemical, from gases or irritating fumes; mechanical, from obstruction; hormonal; infective, from bacteria or viruses; or allergenic due to pollens, dusts, foods or bacteria.

Mechanism and Pathology

While allergic rhinitis, the form to be discussed here, may share with other varieties of nasal activity symptoms which are apparently identical, it differs sharply from them in the very important respect that there is present in such cases a specific sensitization, spontaneous or induced, to substances which have been inhaled, ingested, or absorbed through infective processes. Furthermore, this sensitization is greatly preponderant in the tissues of the upper air passages, since the inhaled antigen reaches these areas first and in greatest concentration. These localities therefore become the depository of the major portion of the specific antibody, the remainder of which may be distributed throughout the body. The reaction between the antibody present in such localized tissue areas and the absorbed antigen which is transported there produces the irritation which is considered responsible for the development of symptoms characteristic of allergic coryza. The mechanism which mediates this reaction is the same as that found in other hypersensitive conditions (Chapter 2).

The increased capillary permeability leads to *edema*, which is the outstanding pathologic feature in allergic rhinitis as in other forms of clinical allergy. The edema involves the mucous membranes of the nose, nasopharynx and eyes, induces sneezing, lacrimation, and swelling of the conjunctivae, and accounts for the bluish-gray boggy appearance of the nasal tissues. Such a pathologic condition is often transitory, both the congestion and the coryza appearing and disappearing as contact with the specific excitant is made and broken.

Unfortunately, in many patients contact with the excitant is more continuous, and more overwhelming, causing the edema in time to become permanent. Especially in infective coryza, where the excitant is bacterial, the bogginess of the nasal tissues may become extensive and chronic, expressing itself in the formation of polyps, redundant and pendulant masses, which develop in both the nose and paranasal sinuses. There may also occur a great increase in the lymphoid tissue of the pharynx and nasopharynx. The tissues, involved originally in a reversible edema, may thus eventually become permanently thickened by the development of fibrous tissue in the submucosa, and by hyperplasia of the mucosa. Eosinophils abound in the nasal secretions as well as in the tissues affected, particularly during or immediately following an attack.

In the majority of cases in which nasal congestion and obstruction are continuous through uncontrolled contact with the excitant, the lack of adequate ventilation and drainage encourages a *secondary bacterial invasion*, which usually leads to the development of an *inflammatory process*. This in turn profoundly alters the picture from one of allergy to one of infection. The blue-gray appearance of the swollen nasal tissues resulting from contact with the allergic excitant may be replaced by a distinct red, caused by the inflammatory response to the invading organisms. The serous discharge may become purulent and the eosinophils, hitherto predominant, may be supplanted by polymorphonuclear leukocytes. These secondary infective changes resulting from bacterial invasion occur more frequently in those patients whose allergic coryza is due to sensitization to air-borne inhalants or to foods. Those persons whose chronic allergic coryza is due primarily to sensitization to bacteria less often acquire such acute secondary inflammatory changes. It is common to note complete freedom from acute and recurring upper respiratory infections, such as "winter colds," in such persons.

Incidence

Allergic coryza, including the seasonal and non-seasonal forms, appears to be the most common form of pathologic respiratory allergy. In a review of 300 consecutive cases of respiratory allergy, 115 or 38 per cent were cases of bronchial asthma, 132 or 44 per cent were cases of pollinosis, while fifty-three or 18 per cent were cases of non-seasonal coryza. Thus, of 300 cases of respiratory allergy, 185 or 62 per cent were cases of allergic coryza.

Etiology

Sensitization of the upper respiratory tract occurs quite independently of the lower. The great majority of hay fever cases, for instance, remain free of asthmatic complications. Many patients suffering from allergic coryza due to dusts or animal epithelia never develop a sensitization of the lower respiratory tract. It is impossible, however, in any discussion to distinguish sharply between the two conditions. The fact remains that coryza is often a prelude to bronchial asthma, a preasthmatic stage or period in which the threat of a potential asthma should be heeded and active steps taken to prevent if possible, or to lessen, the further spread of the sensitization process to the bronchial tract.

While allergic coryza often occurs independently of bronchial asthma, rarely is the reverse true. The two cannot be separated etiologically, clinically or immunologically. They must be considered as components of a single problem, since the causes, the clinical varieties, and the methods of diagnosis and treatment are alike in the two conditions. The discussions on classification, diagnosis and treatment in the chapters upon Non-infective and Infective Asthma apply equally here. Any dissimilarity in symptoms will be due, not to a variance in the allergic mechanism or in the causative factors, but to the anatomic and physiologic differences in the sensitized tissue areas involved.

It may be said briefly that cases of allergic coryza are divided into those whose symptoms are due to non-infective or exogenic causes, and those whose symptoms are due to infective or endogenic causes. In the first group the peccant factors are of seasonal occurrence, such as pollens and molds; and of non-seasonal occurrence,[1, 2] such as dusts, animal danders, vegetable powders, foods and drugs. In the infective group the cause is bacterial.[3] Sensitization to infections of other than respiratory origin occurs but rarely. There is also a mixed group of cases in which sensitization coexists to the non-infective and infective causes mentioned above. This mixed group should not be confused with the individuals suffering from allergic coryza who may develop in the nasal tissues a superimposed acute bacterial involvement of an inflammatory non-allergic character.

Non-infective Causes. The intensity and discomfort of the symptoms in non-infective coryza depend upon the degree of sensitization of the patient and upon the character of the contact, whether it be mild or overwhelming, occasional or continuous. It may be said, however, that nasal obstruction with resultant mouth breathing is probably the worst feature, especially in the cases with exposure uninterrupted for periods of days. In addition to sneezing, severe itching of the nose, tongue, nasopharynx, soft palate and inner ears often occurs. There may be temporarily impaired hearing due to retraction of the ear drums, and a tendency to vertigo and to headache. There is usually a copious, thin, clear nasal secretion, often irritating. The loss of the senses of smell and taste is due to the edema. The mucosa of the lacrimal ducts becomes swollen, leading to obstruction to the flow of tears which are more profuse due to the irritation of the conjunctivae with consequent lacrimal hypersecretion. Itching of the eyes, injection and edema of the conjunctivae and sclera, and photophobia are common. Nasal or labial herpes may develop. Fatigue and malaise frequently occur. These symptoms occur with greater intensity in the patients with acute hay fever than in those with non-seasonal coryza.

The symptoms in the usual case of coryza may occur paroxysmally in sharp sudden bouts, with complete freedom between attacks, or they may be continuous, either mild or severe, depending upon the degree and extent of the uninterrupted contact with the excitant. If continuous, the nasal edema leads to secondary infective changes which often become fixed and stubborn.

While the majority of well established cases present the usual or orthodox array of symptoms, there are occasional patients who may have less than their expected complaints; one may have headaches or nasal obstruction as his sole disturbance, while another may have eye irritation only or episodes of sneezing or vertigo. Many patients complain only of morning coryza. Such a symptom, mild and largely masked, may not be sufficiently distressing in some cases, especially in children, to cause concern. It is dismissed by the parents as a sign of a persistent but not too important "head cold." It is only after the secondary bacterial invasion of these boggy allergic nasal tissues has produced a severe rhinitis or sinusitis that advice is sought.

Inhalants. To the non-seasonal coryza caused by dusts, animal danders, and the like the remarks in the chapter upon the inhalant forms of bronchial asthma are applicable (Chapter 6).

An important form of non-seasonal inhalant coryza is due to sensitization to house dust. This may have a seasonal aspect when patients move to a dust-laden house in summer, or it may appear in the fall and winter involving children especially.[4] Such youngsters are usually free of symptoms throughout the summer months when they are living an outdoor life; but with the coming of cold weather they are thrown into close contact with house dusts, since they are confined in homes or schools where the windows and doors are closed and where the dusty air, often overheated, is kept constantly agitated by the hot air currents from radiators and furnaces. Crowded together in classrooms, the dust-allergic children with their boggy, irritated nasal membranes are particularly susceptible to the intercurrent upper respiratory infections so prevalent in such close quarters. Often it is not the presence of the dust coryza but the development of the recurrent secondary nasal infection that induces the parents to seek treatment. Indeed, in many instances the underlying dust sensitization is so masked by the infection that it is not readily apparent. The history of familial or personal occurrences of known allergic conditions and the unquestionably positive reaction to dust extract by intracutaneous test will aid in establishing the diagnosis. Many catarrhal vaccines, stock or autogenous, gain their reputation for preventing "colds" in such children by being administered in conjunction with house dust extract.

Foods. A food sensitization may manifest itself as an allergic coryza as it has been found to do in bronchial asthma, but it is relatively unimportant, accounting for no more than 2 to 3 per cent of the group.[5] The discussions in the chapters on bronchial asthma are pertinent here, both as to causes, diagnostic methods and treatment. Both the immediate and delayed types of food reaction occur in allergic coryza as in asthma. It should be emphasized that most instances of food coryza appear in children under ten years of age, often associated with urticaria or asthma.

Drugs. Occasionally after ingestion drugs produce nasal allergic conditions. Aspirin, and the aspirin-containing preparations, are important in this respect. Among the vitamin preparations, oral doses of thiamine may result in allergic coryza. The remarks in the chapters upon asthma are pertinent here.

Injectants. In allergic coryza these forms are the same as those in bronchial asthma. Nasal reactions with sneezing, discharge and obstruction are, of course, quite common evidence of the constitutional reaction in the patient tested or treated with inhalant extracts, with foods, or even with vaccines.

Contactants. Such forms of nasal allergy are rare but occur usually in association with contactant forms of bronchial asthma. As has been pointed out in the chapter on Non-infective Asthma, inhalation of the excitant often plays a part and can rarely be ruled out satisfactorily. Suspected as being excitants of coryza by absorption through the unbroken skin are such substances as the essential oils of bergamot, delphinium, rose; mustard (as in mustard plasters); nuts, especially English walnut and Brazil nut; fruits, as orange, banana; vegetables, as celery, parsley.

Infective Causes. In the non-allergic person an active bacterial invasion of the nasal tissues is followed promptly by malaise, chilliness, often by pains in the back and limbs, perhaps by an elevation in temperature and by dryness of the skin and a rapid pulse. There is nasal obstruction, sneezing and a watery thin nasal secretion. There may be lacrimation, redness of the eyes, impairment in hearing, loss of the sense of smell and taste. In the first four to six days the discharge becomes mucoid, then mucopurulent, and the symptoms subside as the infection is subdued. No ill effects usually remain.

This tissue activity may occur in the allergic person also. He has, however, an additional type of response peculiar to himself,[3] which is the result of an inherited capacity for developing sensitization to protein substances, especially those with which he has had intimate overwhelming contact. In him, in contrast with the non-allergic person, the bacterial invasion is not opposed by nasal and sinus tissues which have remained normal, but by membranes which have lost much of their ability to resist through repeated bouts with allergenic substances, such as inhalants, foods or infections. Embarrassed by a diminished and inadequate circulation caused by constant bogginess, the tissues cannot successfully repel the bacterial invasion. There may be no acute response to the infection with malaise, chilliness, elevation in temperature or purulent discharge. There may be no immediately effective protest against the infection which is able thoroughly to entrench itself in the tissues, where its continued presence eventually stimulates the development of a specific sensitization. Through persistent specific bacterial irritation, the nasal tissues, primarily edematous only, and reversibly so, acquire a hyperplastic and polypoid condition which is permanent. Such changes, which also occur in the membranes of the paranasal sinuses, may precede by many years the development of infective asthma. Patients with seasonal or non-seasonal coryza (non-infective), as well as those with bacterial nasal allergy, may develop hyperplastic rhinitis and sinusitis of infective origin.

Non-specific Irritants. Stimulants such as coffee, tea, and especially alcohol, may cause temporary aggravation of the nasal congestion by encouraging the flow of blood to the nasal tissues which are already bogged. Fatigue, emotional upsets or constipation may increase the symptoms in the chronic case. Swimming in fresh water is often irritating, especially in infective allergic coryza. Tobacco smoke, particularly in crowded rooms or cars, is aggravating. Chemical fumes, as of naphthalene or of paradichlorobenzene, in anti-moth preparations are most irritating and should be avoided. Frequently they will produce symptoms almost indistinguishable from pollen coryza.

Silver salts such as mild silver protein, when applied to the nasal mucosa, may aggravate greatly the discomfort, especially if the patient is a sufferer from a pollen coryza; manipulations within the nose with tampons and applicators with their attendant trauma and irritation often cause more harm than good. The same can be said of the frequent use of all decongestive or shrinkage drugs as nasal sprays or drops (epinephrine, ephedrine and privine).

Diagnosis

History. A complete and comprehensive history is the most important diagnostic aid in solving problems in allergic coryza, as it is in other forms of clinical sensitization. The discussion of the points important in the taking of the history in bronchial asthma applies here (pp. 36, 114). The attacks should be investigated as to their paroxysmal or continuous nature, their duration, severity, relationship to meals, time of day, days of the week and season. With one eye upon the calendar, the investigator must learn whether the months of pollen production are related to the occurrence of symptoms; or whether the attacks seem related to earlier periods in the spring or later in the fall, the turn of the seasons when weather variations with the occurrence of dampness and cold aggravate the patient with infective coryza. The midwinter periods are important too, since the infective cases are often aggravated at that time.

The effect of environment upon the coryza is important, the inhalant types, seasonal and non-seasonal, showing marked improvement upon shift to the proper physical surroundings. The infective cases are not so readily influenced, unless there be a radical change in climatic environment.

The attacks of coryza may occur paroxysmally after periods of complete freedom. This is the usual pattern when the excitant is an airborne inhalant or a food occasionally encountered. Or the attacks may be continuous when allergenic contact is uninterrupted, as may be the case with many inhalants and foods and is almost always the case with bacterial products of nasal or sinus origin.

It is very important to ascertain whether the attacks of sneezing, coryza and nasal congestion are accompanied by discomfort of the eyes, such as itching, lacrimation, injection of the cornea and edema of the mucosa of the lids and cornea. Such complications would tend to implicate as the cause air-transported excitants such as pollens or non-seasonal inhalants, as opposed to foods or infections. Itching of the soft palate, nasopharynx, tongue and buccal mucosa are more frequent in pollen coryza.

In coryza, as in bronchial asthma, occasionally a dietary factor may be the specific cause. A detailed analysis of the patient's diet is essential. As in asthma, a study of the patient's whims, excesses and indiscretions in eating is necessary. A food contact may be followed immediately, within twenty-four hours or less, by symptoms of coryza, in which case the skin tests with the excitant will usually prove helpful. If the symptoms of coryza are delayed, not occurring until a period longer than twenty-four hours has elapsed, the skin tests with the excitant will usually prove negative. Food-sensitive cases may thus be divided into those that are skin-sensitive, with an immediate reaction time, and those that are skin-negative, with delayed reaction time. This has been fully discussed in the chapter upon non-infective asthma.

Cases of allergic coryza due to bacterial sensitization are found to be similar to the second of these groups, since they are skin-negative with a delayed reaction time. The time interval between contact with infection and development of symptoms cannot be measured very closely. That there is a delayed interval is indicated by the clinical observation that twenty-four hours or longer usually elapse before any exacerbation from respiratory infection in the patient with infective coryza or infective asthma is followed by a flare of his allergic symptoms. In the delayed types of food allergy, it is thought that often the time lag may represent the interval required for the breakdown of the ingested food protein into the digestive products which are really the antigenic substances to which the patient is sensitive. In bacterial sensitization the time lag may be utilized for similar deterioration processes. This idea would seem to be at least partially strengthened by the observation that while patients with an infective allergy may exhibit an exquisite degree of sensitiveness to respiratory organisms present in autogenous or even stock vaccines, intracutaneous test with such material does not produce the immediately positive wheal, but rather the papule with erythema which occurs only after several hours. Further, a time lag of several hours usually occurs between the administration of an excessive amount of the vaccine by intracutaneous test or by parenteral injection, and the development of constitutional or generalized symptoms. This, of course, is in sharp contrast to the distressingly prompt constitutional effect which may occur in the person who has been given an intracutaneous test or an injection with an inhalant or food allergen to which he gives an immediate wheal reaction.

Laboratory Examinations. In the simple uncomplicated case of allergic coryza laboratory procedures give little help. The results of the urinalysis, the chemical blood analysis and the estimation of the sedimentation rate are not abnormal. The blood count shows an increase in eosinophils during or immediately after an attack. A smear of the nasal secretions may show a preponderance of eosinophils. Such an increase is a clear indication of the allergic nature of the coryza, but it does not provide a means of differentiating between non-infective allergic rhinitis (of inhalant or food origin) and infective allergic rhinitis (of bacterial origin) for in both eosinophilia may be found, usually greater in the bacterial allergy. It serves chiefly to differentiate between allergic and non-allergic nasal irritations. Roentgenograms of the nose and sinuses in chronic allergic coryza of infective and of non-infective origin usually show thickening of the membranes which is symmetrical and in advanced cases extensive and uniform, involving all sinuses. Should the involvement be limited to a single focal point, as an antrum or to one side of the head, infection rather than allergy should be suspected.

Technical Procedures. The methods outlined in the chapter upon Non-infective Asthma (p. 117) are indicated in these cases, such as the skin testing procedure, which is, of course, useful only in cases with immediate reaction time. It is without value in the skin-negative group in which the history, clinical tests, trial and error methods, elimination diets and food diaries must be resorted to. In the bacterial cases, the procedures discussed in Chapter 7 for problems of infective asthma are to be employed.

Differential Diagnosis. While a carefully obtained history and the skin testing procedure verified by clinical test and aided often by films of the sinuses will usually be sufficient for establishing the presence of a coryza of allergic origin, it should be recalled that nasal discharge may occur in other conditions.

In the child a persistent discharge, often unilateral, at first mucoid, then purulent, may prove to be due to a foreign body such as a bean or a button in the nasal cavity, as a thorough examination will usually show. Nasal polyps, septal spurs, hypertrophied turbinates may also produce mechanical obstruction. Extremes of heat or cold may provide the physical factor in the production of coryza or sneezing.[7] It is not uncommon to obtain from a patient a description of vigorous attacks of sneezing with nasal congestion and discharge which occur when he proceeds from a room with high temperature to one with low temperature, or vice versa. Even the change in temperature encountered in the summer when walking from sunshine to shade will produce sneezing attacks in some persons. Strong light rays, such as in summer sunshine, may produce coryza and sneezing attacks in hay fever patients to such an extent that spectacles with dark lenses are helpful.

The initial catarrh of certain virus diseases may be mistaken for an allergic coryza. This is true of acute infectious coryza (the common cold) and of influenza. Pronounced catarrh with sneezing and congestion of the eyes may be the first evidences of another virus disease, measles, and may be followed by cough and by irritation of the lymphoid tissue of the nasopharynx, leaving enlarged tonsils and adenoids.[8] In the initial stages, such virus conditions may be confused with allergic coryza, but the appearance of the febrile reaction soon clears the picture.

Coryza due to endocrine disturbances may be related to the premenstrual phase[9] or to menopause and is said to be due to sensitization to endogenous allergens produced within the organism by the endocrine glands.[10]

The patient with an allergic coryza, particularly hay fever, finds many secondary non-allergic factors which intensify the attacks of sneezing and nasal congestion. Often disturbing are chemical fumes, especially those of drying paint, lacquers and varnishes; also moth preventives generally, as paradichlorobenzene, naphthalene flakes, camphor balls; insecticides and sprays for rose bushes, fruit trees, other vegetation; dry cleaning fluids, fumigating and illuminating gases; gas from mechanical refrigeration units. The partially dried ink in the newspaper read at breakfast time may cause non-specific morning coryza.

Toilet articles may contain irritating substances, such as perfumes and odors in soaps, in hair tonics and lotions, and chemical fumes in nail lacquers. Finely divided soap particles, as in powders or flakes, or lather of shaving soap, often cause pronounced sneezing. The fibers and lints from paper handkerchiefs and towels may produce mechanical irritation of the nasal membranes.

Treatment

General Measures. In common with all other varieties of allergic conditions, the elementary principle in treatment is that of shunning the exciting substance. This principle of avoidance and escape has been discussed fully under Non-infective Bronchial Asthma, but it is well to repeat the fact that while evasion of the causative agent is essentially a passive procedure, indeed a compromise, it is usually far easier to relieve allergic discomfort successfully by such a plan than it is to influence, by immunizing procedures, the inherited allergic predisposition. If the coryza is due to removable inhalant substances, such as the dog or horse, or to foods as egg, the simple omission of these substances from the environment, physical or dietary, may be sufficient. If contact cannot be readily avoided, specific therapy, as discussed under Non-infective Asthma, may be attempted. (Chapter 6.)

While the same rule of avoidance holds true also for the infective cases, its observance is less simple due to the difficulty of ridding the nasal tissues of the specific causes which usually are present also in the paranasal sinuses. These causes, the organisms which have invaded the nasal and sinus areas, can be eliminated only by removing the tissues which they have involved, a procedure never simple, and due to the topography of the region, never complete, hence rarely entirely satisfactory.

The patient suffering from an infective type of allergic coryza and sinusitis possesses in common with patients having other forms of clinical sensitization the characteristic of developing pronounced allergic symptoms after contact with relatively minute amounts of the excitant. Hence, following the surgical removal of the bacteria-ridden tissues, accomplished as completely as possible, the organisms in the residual amounts of tissue may still be sufficient in number or in activity to cause a continuation of the allergic symptoms. Only over a period of many months may it be possible to overcome the remaining infection through recuperative processes whose deliberate nature disappoints the patient, who is led to expect prompt and permanent results by his experiences after such operations as the excision of the appendix, tonsils or gallbladder.

Vaccine Therapy. In practically all cases of infective rhinitis, attempts at immunization should be made with the use of bacterial vaccines, stock and autogenous, the latter being prepared from cultures of the sinus, nasal or bronchial secretions. The procedures are the same as those discussed in the chapter on Infective Asthma (p. 151).

Therapeutic Agents. In allergic coryza the principal need for drug therapy is in relieving the edema of the nasal tissues. The decongestant, autonomic drugs used for this purpose are amphetamine (benzedrine), which is supplied in small inhaler tubes; ephedrine and ephedrine-like preparations; and epinephrine. These medications are employed in sprays or drops in aqueous solution. Ephedrine, incorporated in a tragacanth type of jelly, is sometimes preferred. The drugs, when applied to nasal mucous membranes, cause moderate contraction of the capillaries and thus, by diminishing the hyperemia, may reduce the swelling and congestion for varying periods depending upon the degree of congestion and the potency of the therapeutic agent. In the severe cases the effect is fleeting or absent, so that there is often the temptation to use a greater and greater quantity of the preparation, increasing degrees of tolerance demanding it. Such unrestricted use should be condemned since it frequently leads to atony of the capillary walls, not only rendering them unable to respond to further local applications but actually increasing the bogginess. There may occur, furthermore, the unpleasant systemic effects of nervousness, tremor, tachycardia, palpitation and symptoms of the anxiety complex. In the unsupervised patient who has employed excessively in the nose a medication of the decongestant type, both nasal congestion and temperament will often rapidly improve upon discontinuing the drug. There is much to be said in favor of the suggestion of making decongestant drugs available only on prescription.[11] It should be recalled that occasional sensitization of the nasal mucosa to ephedrine and to the sulfa group of drugs may develop from continuous local applications of these preparations. Epinephrine and cocaine, used locally in the nasal cavity, may occasionally cause violent sneezing and congestion.

Ephedrine by mouth may be unsatisfactory for the relief of nasal edema, since the unpleasant constitutional effect will often develop upon oral dosage before any satisfactory local influence upon the nasal mucosa is evident. Atropine, 1/150 grain, or tincture of belladonna in 10 minim oral doses, may prove useful in checking the excessive rhinorrhea which develops in the acute attacks. Cold compresses upon the face are often helpful in relieving nasal congestion by lessening the blood flow to the nose. For the same reason, by sitting in a tub of water as hot as can be tolerated for ten to fifteen minutes, to draw blood to the lower portion of the body, the patient may experience relief from the nasal congestion.

The reports on the oral use of antihistaminic drugs such as pyribenzamine (n′-pyridal-n′-benzyl-n′-di-methyl ethylene diamine mono-hydrochloride) and benadryl (beta di-methyl amino-ethyl-benzhydryl-ether hydrochloride) indicate that they may prove helpful in reducing nasal and sinus congestion of allergic origin. Evaluation of these drugs as well as anthallan must await more extensive clinical experience.

Results. The results of treatment are dependent upon the type of case involved. The simple inhalant cases whose excitant is recognizable and removable, before secondary infective changes have occurred, do well. The bacterial cases respond to treatment less satisfactorily. It may be stated that the results obtained in the several corresponding forms of asthma are indicative of the degree of success to be expected in the treatment of allergic coryza.

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Section IV

ALLERGY OF THE SKIN

13. Allergic Dermatitis

ROBERT A. COOKE

In no special field of medicine has the concept of allergy exerted a greater effect than in dermatology, for it has provided the explanation as well as a means of etiologic diagnosis for certain of the edematous and inflammatory lesions, particularly that most frequent lesion of all, the dermatitis not due to trauma nor to microbic invasion, formerly spoken of as eczema, now generally designated allergic dermatitis.

THE NORMAL SKIN

The skin is a complex cellular structure which, in addition to its esthetic value and protective action, has many important functions. It is an organ estimated to constitute nearly 15 per cent of the total body weight, and is as vital to life and well-being as any other of the principal organs of the body.

Functions. These may briefly be enumerated as follows:

Protection.
Regulation of heat.
Secretion—Sweat and sebum.
Sensation—Heat, cold, touch, pain.
Respiration.
Absorption—Ultraviolet ray, chemicals.
Excretion—Water, urea, carbon dioxide.
Immunization—Sensitization.

From the standpoint of allergy the function of the skin in relation to the processes of immunization or sensitization is most important.

Immunization. Evidence of the action and reaction of the skin is seen in the response that may be obtained to tuberculin, brucellergin, typhoidin, trichophytin and other fungus preparations, and to the polysaccharides and proteins of the pneumococcus. Such specific skin reactions occurring in persons previously infected indicate the bio-cellular activity of the skin even though no skin lesion is apparent as a part of the disease.

The Shwartzman phenomenon also illustrates an immunologic cutaneous response. In 1928 Shwartzman[1] showed on experimental animals that the intracutaneous injection of a typhoid bacillus culture filtrate "prepared" the injection site so that the intravenous injection of the same filtrate twenty-four hours later gave rise to a local reaction within four hours, which later went on to hemorrhage and necrosis. The significance of the reaction is still not known.

The Arthus phenomenon, described in 1903,[2] represents a type of local anaphylaxis or induced allergy, that is, an antigen-antibody reaction. Repeated subcutaneous injections of horse serum in rabbits, at first devoid of effect, ultimately give rise to a local reaction at an injection site where there develops, after several hours, local heat and swelling which may go on to necrosis. Similar phenomena have been seen in man after several subcutaneous serum injections, but this condition, always rare, is still more so today as serum therapy is being replaced by chemotherapy.

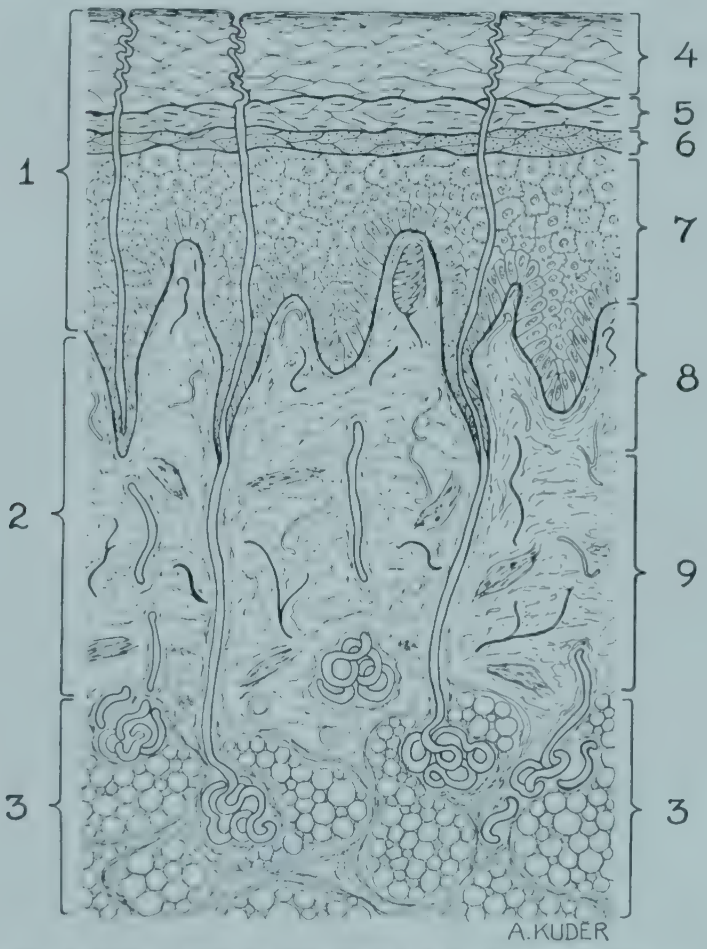

Fig. 17.—Semi-schematic vertical section of the skin. 1, Epidermis; 2, corium; 3, subcutaneous tissue; 4, stratum corneum; 5, stratum lucidum; 6, stratum granulosum; 7, stratum mucosum; 8, pars papillaris; 9, pars reticularis.

The immediate urticarial wheal and the delayed dermatitis following the intradermal and patch tests respectively with the proper allergens clearly show the cutaneous response when the cells are appropriately sensitized.

Cellular evidence of the immunologic activity in the skin is portrayed in lesions of various dermatoses by the presence in the tissue of eosinophile cells, both poly- and mononuclear types, and of epithelioid and endothelioid histiocytes of reticulo-endothelial origin.

Histology. There are many layers of cells in the skin, semi-schematically represented in Figure 17. These may be described briefly according to accepted nomenclature as follows;

1. Epidermis or Cuticle
   - Stratum corneum—keratin layer.
   - Stratum lucidum—eleidin-containing.
   - Stratum granulosum—keratohyalin granules.
   - Stratum mucosum or rete—prickle cells.
2. Derma, Corium, Cutis Vera, or True Skin
   - Pars papillaris.
   - Pars reticularis.
3. Subcutaneous Tissue (Panniculus adiposus)

The epidermis is closely attached to and fits over the papillae of the corium. There are no blood or lymph vessels, but nerve fibers are abundant. It is perforated by the hair and by sweat ducts (pores).

The derma is made up of connective tissue, collagen and elastic fibers, blood and lymph vessels, nerves, sweat and sebaceous glands, hair and hair follicles.

The subcutaneous layer is attached to the tissues beneath and more or less gradually blends into the corium. It is not distinctly demarcated. It contains blood and lymph vessels, nerves, some sweat glands and hair follicles. It is a loose areolar connective tissue with varying amounts of fat deposit.

ALLERGIC DERMATITIS

Under this heading are considered those inflammatory lesions of the skin which are believed to be due to an allergy. The condition may be acute but more often is chronic with exacerbations. There is itching with superficial desquamation and serous exudate on the surface or in the epidermal layer. The lesions may be erythematous, papular, vesicular or pustular, any one or all of which may be present at one and the same time. They may be isolated, but generally coalesce into larger or smaller infiltrated areas. In the chronic cases the skin becomes dry and thickened generally (lichenification) with a tendency to crust and crack.

In no important group of commonly accepted diseases of allergy is our knowledge more scanty and more superficial, and the dermatologic and allergic literature more contradictory and confusing, than in that group designated as allergic dermatitis.

In spite of the fact that extensive pathologic studies have been made, and some of the specific etiologies are known, no established factual basis for an immunologic mechanism which can mediate the reaction has been disclosed. As a result, dermatitis as an allergic phenomenon, that is an antigen-cellular-antibody reaction, rests upon hypothetical but not unsubstantial grounds. It is significant that as yet there has been no successful effort to correlate pathology and etiology with immunology, and until this is done no important advance toward a solution of the problem is likely. What is sorely needed is a cooperative venture by the pathologist, the immunologist and the clinician.

Nomenclature

There is no consensus as to what constitutes dermatitis in contradistinction to eczema, as these terms are presently used in dermatologic literature. The reason appears to be that there is no essential clinical, histologic or etiologic basis for a distinction. The lack of fundamental knowledge and the attempt to fill the gap by a descriptive but confusing nomenclature have done more to retard than to advance the subject.

It is necessary to define the terms that will be used in the discussion of dermatitis resulting from what we regard as an allergic reaction. There are many forms of dermatitis due to physical, chemical or mechanical trauma, and to infections of the skin that are not based on an antigen-antibody reaction; hence I shall use the limiting and qualifying word "allergic" for those forms which are assumed to be allergies. Many dermatologists would like to be rid of the word "eczema," for it has acquired so many ill-defined meanings. It would be a happy solution if they could agree to make the word "eczema" apply to allergic dermatitis of external and internal origin but in the absence of such accord I shall refrain from its use.

At present there are supposed to be two separate types of allergic dermatitis; therefore a more difficult problem is posed by the question of a term for the external contact type and for the internal contact type, this latter being exemplified by the so-called infantile eczema and often called "atopic dermatitis." In the discussion to follow I shall present my reasons for believing these two conditions are immunologically the same. There is some clinical advantage in allergic dermatitis in indicating the source of the allergen and mode of contact, whether external or internal, just as there is in asthma, which is often designated as inhalant or food asthma, but this does not imply that there are any immunologic differences in food and inhalant asthma, nor should different methods of contact in dermatitis imply differences in immunology.

One might attempt to coin a word or phrase to indicate the lesion arising from external contact with an allergen as opposed to the internal contacts that are of hematogenous or lymphogenous origin. The words extrinsic and intrinsic already accepted for asthma seem to be most satisfactory to convey the idea of the source or portal of entry. An objection possibly presents itself in that foods and drugs which are extrinsic causes for asthma would be intrinsic, that is internal contactants, for dermatitis. But no more explicit and meaningful terms come to my mind than "extrinsic" for the lesions from allergens externally contacted, and "intrinsic" for those from within, although such words as epidermal or dermal respectively are perhaps equally good. So, with an aim for accuracy and clarity, I shall indicate all forms of dermatitis due to allergic reactions as *allergic dermatitis*, meaning to exclude all other forms of dermatitis, traumatic or otherwise. The adjectives *extrinsic* and *intrinsic* may then be used merely to indicate contact from without and contact from within respectively.

Both intrinsic and extrinsic allergic dermatitis are inflammatory lesions of the skin and are due to an allergy which has the same immunologic processes and factors. It is natural that there would be minor pathologic differences depending upon whether the living cells of the epidermis or those of the derma are first brought in contact with the allergen. In every severe lesion the derma is involved, with edema, congestion and round-cell infiltration. The epidermis shows edema and thickening of the stratum mucosum. That the changes are greater in the epidermis in the one case (external contact), and in the derma in the other (internal contact), is dependent on which layer receives the first and major exposure to the allergens, and in all cases the differences are merely quantitative.

My objection to the term "atopic dermatitis" is that the meaning of the word atopy has been confused, and its present use clearly implies that the allergens giving immediate wheal reactions in certain patients with dermatitis have an etiologic significance they do not possess (p. 238).

This suggested nomenclature is simple and descriptive, and indicates the method of contact, whether from without or from within, and therefore the sources of possible agents of reaction, at the same time indicating the identity of the immunologic reaction which I believe to exist in the two forms. It is definitely tentative as all classifications must be until validated or invalidated by further knowledge.

The Basis for Allergy in Dermatitis

Granted that there are many causes, including physical, chemical and mechanical, for the lesions of dermatitis, nevertheless there are sound reasons for the present assumption of an antigen-antibody mechanism (allergy) for certain of them. One reason is that a skin lesion may be induced by substances not primarily irritating, and another is the significant association with other accepted allergies.

Induced Sensitization. Certain substances not reactive on normal skin may produce a dermatitis in persons in whom prior contact has established a basis for sensitization. Many years ago, when Spain and

I[3] were studying dermatitis venenata, we showed that the alcohol-soluble fraction of poison ivy (Rhus toxicodendron), when applied to the skin for several days in varying dilutions by the "patch test," produced the typical lesion of dermatitis, and that those persons clinically very sensitive in general reacted to the weaker solutions. Spain[4] showed that 65 per cent of all adults reacted on first test with the oil, but that infants did not react to the primary application, so that the lesion was not due to a primary escharotic effect of the oil. Low[5] recorded experiments with primula; the leaf when first applied for several days gave no local reaction, but when the experiment was repeated several weeks later a dermatitis was produced on the second day. Heinbecker[6] was able to test Eskimos, of course never previously exposed to ivy, and found that adults gave no reaction to the first and only application of this oil; thus it is not a physiologic reaction of adults. Unfortunately a unique opportunity was missed since Straus'[7] illuminating studies had not then been done. Straus confirmed the observation that infants a few days old did not react to the first application of ivy oil, but when a number of his cases were retested several weeks later a positive response was obtained in 75 per cent.

In other words, it may properly be assumed that the first application stimulates some cellular activity which results in the formation of a mechanism, the hypothetical antibody, which produces a state of sensitization not only locally at the site, but of the skin generally. The lesion of reaction is no doubt determined by the character of the antigen, the nature of the antibody and the type of cell or part of the cell that reacts. None of this has been proven, but it is known that the reaction is an exudative lesion of the skin, and that it is a *delayed reaction* which never appears before twenty-four to forty-eight hours after contact. No antibody capable of specifically sensitizing normal skin to respond with the characteristic lesion on test has ever been demonstrated in the serum of reacting persons; hence it is postulated as a purely *cellular antibody*.

It would appear, then, that as a result of contact a mechanism of reaction has been established with oil of ivy, and as this has been shown to exist in a large majority of human beings (about 75 per cent in the United States) it must be regarded as physiologic or normal for man, and it is not influenced by familial and hereditary factors. This frequency is analogous to that which obtains in the artificial sensitization of man with horse serum, which is also a physiologic response for the species, but there the analogy ends, for immunologically, clinically and histologically there is no resemblance.

Since about 75 per cent of the adults in the United States are reactive to the oil of ivy and adult Eskimos are not, it may be assumed that sensitization follows casual contact with this common plant. This widespread effect is not true for the majority of the important allergens of contact dermatitis; hence it may be inferred to depend upon the chemical structure of ivy oil, making it highly antigenic, or upon a special property of human epithelial cells, or upon both these factors. That must be left to the future to decide.

Association with Other Allergies. There is a noteworthy clinical association between the so-called infantile eczema and such other definite allergies as asthma and hay fever. My studies[8] have shown that at least 50 per cent of these allergic infants with dermatitis already have or will develop clinical asthma or allergic rhinitis before their tenth year, and the cases of asthma with an age of onset under ten years give a past history of dermatitis in about the same percentage. Also, the history of patients who had allergic dermatitis early in life shows that an allergy of one type or another is found in the family with the same frequency that exists in the family of patients who have hay fever and asthma. This is in accord with the general experience of others who have studied the subject. Blood eosinophilia is as frequent and as high in these patients as in those with hay fever and asthma.

It may be concluded then that, according to the present conceptions and for reasons which appear logical and sound, both intrinsic and extrinsic dermatitis may be regarded as a phenomenon of allergy that is based upon an antigen-sensitized cell union.

Immunopathologic Relationships

There is seemingly a lack of appreciation of the different immunologic and pathologic types of antigen-antibody reactions (see Chapter 2) which produce totally different clinical expressions, as for example hay fever and dermatitis, which may and often do appear concurrently or at separate times in one individual. They are proven, as in hay fever, or assumed, as in dermatitis, to be based upon a specific cellular antibody mechanism which identifies them as allergies, but this is the limit of their resemblance.

The confusion that exists today regarding allergic dermatitis is due to (1) a misinterpretation of the relation of allergens inducing immediate wheal reactions to allergic dermatitis, and (2) the misconception that there is an essential immunologic difference between the skin lesion caused by external contactants (extrinsic allergic dermatitis) and the lesion generally referred to as infantile eczema or atopic dermatitis (intrinsic allergic dermatitis).

(1) The Relation of Allergens Inducing Immediate Wheal Reactions to Allergic Dermatitis. It is a fact that, in infants with dermatitis, a history of past or present allergy, either asthma, allergic coryza or urticaria, is found frequently in antecedents and siblings, that asthma or some other allergy develops in over 50 per cent of these patients when observed over the years, and further that many of these patients with dermatitis have immediate wheal reactions to various allergens when skin-tested by direct or passive transfer methods. Hill[9] states that in 100 atopic (eczema) infants less than one year old, eighty-six reacted by direct skin test to egg, twenty-six to milk and seventeen to wheat. These results are common observations and well established facts, and it was on account of such findings that the term "atopic dermatitis" was first used. It is unfortunate, for the word "atopy," as was stated, is used by some to indicate the hereditary allergy factor as originally intended, by others to signify not only the existence of a wheal-reacting allergy but that the positive test has diagnostic significance. By many it is used interchangeably. Unhappily this has resulted in a rather general use of the intradermal or scratch test as a diagnostic procedure, not only in the so-called infantile eczema but in many other types of dermatitis.

It is my considered opinion that the "atopic reagins," which in fact are the skin-sensitizing antibodies of the immediate wheal reaction, have neither diagnostic nor immunologic import in allergic dermatitis. If this is so, then the term "atopic dermatitis" is confusing, without meaning, and should be discarded.

As a basis for this opinion I may cite the studies which Hampton, Wing, Boker and I[8] have made on typical cases of the dermatitis of infancy and early childhood in the Allergy Department of the Roosevelt Hospital. In one group of sixty-odd cases, tests by the method of passive transfer were done. The serum of over half of the patients gave positive and usually multiple wheal reactions; often there were as many as thirty positive tests, to both foods and inhalant substances, while the balance gave no reaction. The family incidence of allergy was equally divided between the reactors and non-reactors. Asthma as a concurrent allergy occurred in ten patients under three years of age—in six of those with positive passive transfer tests and in four with negative tests. The clinical picture of dermatitis and its course, however, were the same in the two groups.

A second selected small group of twenty-seven of these patients was hospitalized for dietetic study. Fifteen of these had other allergies—asthma, urticaria or allergic coryza. All the patients were tested by passive transfer, and the serum of seventeen gave typical immediate wheal reactions to one or several foods. In thirteen the positive tests were verified in part (one or more) by direct skin test. It was our intent to prove or disprove the causal relationship of the allergen giving an immediate wheal to the dermatitis in each particular reacting case. Except for the nine patients acutely sensitive to egg, peanut or honey, the foods giving positive skin tests could be eaten abundantly and continuously without any exudative skin reaction. Egg, peanut or honey was fed in whatever amounts were possible. If eaten and retained, urticaria appeared promptly—never dermatitis—and these patients could eat all other skin test-reacting foods in quantity and indefinitely without developing any dermatitis. Fourteen of the seventeen patients with positive skin tests to foods were also skin test-positive to inhalant allergens. Under hospital conditions these factors could be excluded as causes of dermatitis.

In this particular group, and since then in considerably extended studies, there has been an entire absence of any correlation between the allergens producing immediate wheal reactions and any exacerbations of the skin lesion when the reacting food was eaten in quantity and over long periods. For this reason my conclusion has been that there is no causal relationship between such allergens and dermatitis, and therefore skin testing by the scratch or intradermal method for immediate wheals is not a correct approach to a diagnosis of the cause of allergic dermatitis.

A moment's consideration will explain this. The scratch or intradermal test, when positive, gives rise to a prompt (within twenty minutes) edematous wheal. Proper contact with the reacting antigen in patients *clinically* sensitive likewise gives rise to an immediate clinical reaction of the same edematous type, such as asthma, hay fever or urticaria. This is an inherent property of all such reactions and is the only response of which this type of allergy is capable. On the other hand, all of the dermatitic lesions of allergic nature which we know of are delayed (twenty-four to forty-eight, and even seventy-two hours) inflammatory and exudative lesions involving the epidermis and derma—not wheals. In 1932 I expressed my ideas on this as follows. "It must be borne in mind that with the tests we should seek to duplicate the essential (histologic) characteristics of the clinical reaction. Lack of regard for this principle has flooded medical literature with a mass of misinformation."[10] This observation has been recognized in the more recent publications but apparently only so far as external contacts are concerned.

It is my opinion, supported by clinical experience, that the skin-sensitizing antibodies for the immediate wheal reaction so frequently found circulating in the blood of infants with allergic dermatitis are either an indication of an existing allergy of the edema type or a portent of such allergies to come—the future asthma and rhinitis or urticaria. Their presence does not necessarily mean a clinical allergy, and never indicates a dermatitic one.

The meaning, however, of the clinical association of the allergic dermatitis, especially noted in infants and young children, with the immediate wheal-reacting allergies as asthma and hay fever is certainly not clear. All that can be said is that they are two different and distinct types of reaction occurring in those predisposed by nature or inheritance to an allergy of one or several types. A comparable situation is seen in a patient with asthma due to both pollen and infection. Here we have one clinical allergy with two etiologies, each based upon a different immunology. This is a common observation.

(2) **Relation of Intrinsic to Extrinsic Allergic Dermatitis.** *General Considerations.* The assumption seems justified that extrinsic dermatitis (external contact type) is an antigen-antibody reaction in the sense that there is a special mechanism which permits substances innocuous to normal skin to produce an inflammatory reaction in the epidermis of so-called sensitized persons. In the intrinsic type the evidence for allergy is based upon the close clinical association with known allergies, the frequent blood eosinophilia and the positive patch test in some cases.

Although an antigen-antibody (allergic) basis for both is acceptable, there is no doubt that differences exist which are not absolute but hold only for the general average of cases in each group. These may be tabulated as follows:

Factors	*Intrinsic Type*	*Extrinsic Type*
Pathogenesis	Frequent hereditary background	Rare hereditary background
Etiology	Spontaneous	Induced
Primary area	Unexposed skin	Exposed skin
Associated allergies	Frequent	Rare
Eosinophilia	Frequent	Rare
Age of onset	Before puberty	After puberty

In spite of this rather imposing list it is a question whether the differences are really fundamental or represent quantitative variations, for the lines are not drawn hard and fast between them.

Granted that dermatitis from external allergens is induced by prior contact, this has not been readily or generally accomplished except in the case of oil of ivy. Schwartz and Tulipan[12] state that in twelve likely industries the yearly occurrence of occupational dermatoses is but a trifle over 1 per cent, and this may include some non-allergic cases due to chemical or physical agents. This percentage is reasonably comparable to the incidence of sensitizations to the sulfa drugs, and is not very different from the estimated incidence of allergic dermatitis in infancy.

The extrinsic dermatitis (external contact type) may occur only after extensive and prolonged contact, but in occasional persons the stimulation is minimal, as for example in one patient in whom a dye sensitization developed and persisted for years after a single patch test application of the dye for experimental purposes. These facts indicate that the few persons with dermatitis from known contacts other than ivy oil are "susceptibles" without implying that the susceptibility is *or* is not based on heredity. Certainly it is not physiologic, as in the case of dermatitis venenata, and because of its infrequency is not dependent wholly upon the potency of the allergen. It must therefore depend to a definite extent upon the constitutional make-up of the individual, even though there is no history of familial allergy or other evidence of an allergic constitution.

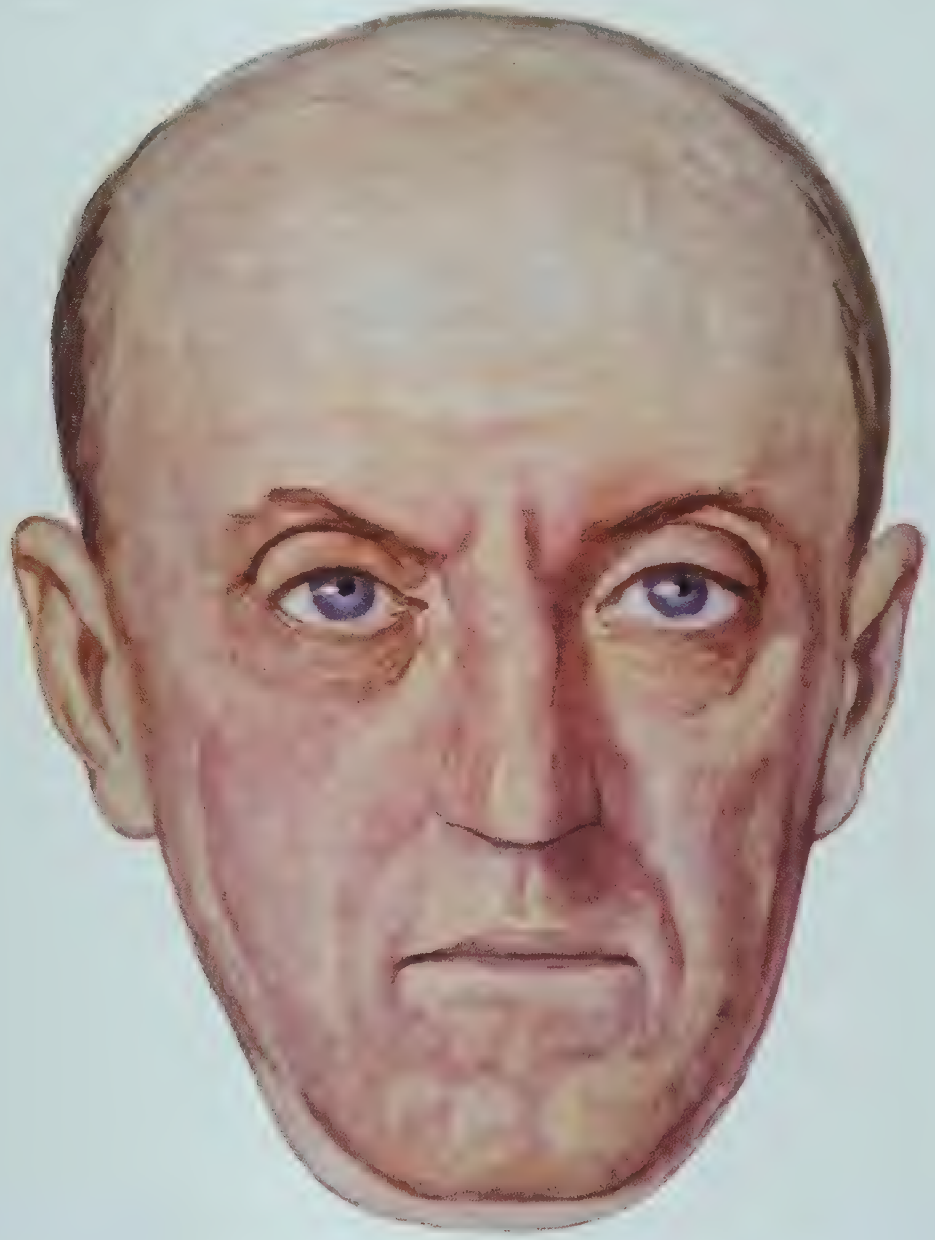

Fig. 18.—Case 1. M.C. Extrinsic allergic dermatitis—mercury.

Dermatitis due to external contact together with a wheal-reacting type of allergy and with dermatitis of intrinsic origin is not rare. However, the pre-existence of intrinsic dermatitis certainly does not predispose to or render easy a cutaneous sensitization to any and all external contacts. They are seen together but only in about the same proportion as would be expected according to the incidence of each in the general adult population.

In extrinsic dermatitis (external contact type) the lesion is of necessity at the point of allergen contact with sensitized cells, as it is in all allergy, for example hay fever. The fact that the lesion is more general in the intrinsic type only indicates the more general distribution of the allergen to the entire skin through blood and lymph, and is not of basic significance in so far as the immunologic mechanism is concerned. The additional fact that extrinsic dermatitis is not infrequently diagnosed by patch test is not important, since the probable causes are obvious, and if the skin sensitization is general it is relatively easy. In the intrinsic type, however, relatively few cases are diagnosed by patch test because the allergens are not so easily identified, and our minds have been set on proteins as the chief etiologic factors.

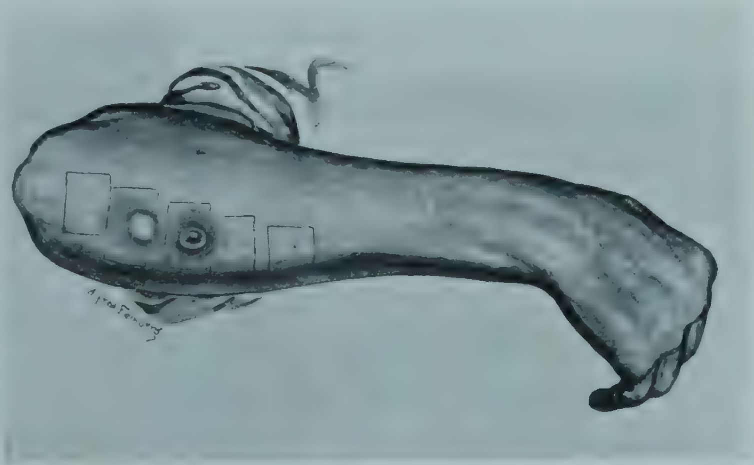

Fig. 19.—Case 1. M.C. Positive patch test with mercury and drug containing mercury.

Immunologic Considerations. The question for consideration here is whether it is necessary or correct to assume a distinctly different immunologic basis for the extrinsic and intrinsic allergic reactions of the skin. The best approach to this discussion will be through the brief citation of a few illustrative cases.

Case 1. M.C., a male physician aged fifty, in winter, about five years prior to his first consultation, suddenly developed an itching eruption of the face and hands. It cleared up whenever he left home, and reappeared two or three days after his return. Once, after taking a calomel pill, he had an acute general dermatitis. As this patient dispensed his own drugs his usual exposure was through external contact. Patch tests were positive after twenty-four hours to the drugs he handled containing mercury and salol (Figs. 18 and 19).

Case 2. H.W., a male bookbinder aged thirty, was admitted to the hospital complaining of recurring attacks of acute exudative lesions of the skin. These gradually subsided with local treatment, and he was discharged improved with a diagnosis of acute dermatitis, cause unknown. On account of a persistent skin lesion of the hands and forearms he was referred to the Allergy Clinic. It was presumed that he was sensitive to a mercury preservative in the glue he used in the binding of books. He was reactive by patch test to the glue and to mercury. It was then discovered that the acute attacks of dermatitis were due to a mercury-containing laxative.

Under the usual conditions of exposure these two cases are typical examples of extrinsic dermatitis and both patients had essentially the same skin lesion when mercury was ingested. The only difference was in the general distribution when the drug was taken by mouth.

These cases illustrate that the method of contact, whether external or internal, is immaterial in the production of a dermatitis.

Case 3. C.G., a woman aged thirty-eight, had no family or other allergy history. For the past four summers prior to examination this patient had an itching eruption of the skin about the right eye only, which began in June and lasted until October. After she was placed on a diet excluding summer fruits and vegetables, the rash cleared in a few days. It reappeared on the third day after eating tomatoes on three separate trials. Patch tests on the extremities and trunk with all sorts of tomato preparations were negative. Fresh tomato juice applied nightly to the right and left eyelids reproduced the typical lesion only on the lids of the right eye at the end of the second day. Intradermal tests on the arm with extract of tomato did not produce any immediate wheal reaction or even a delayed one.

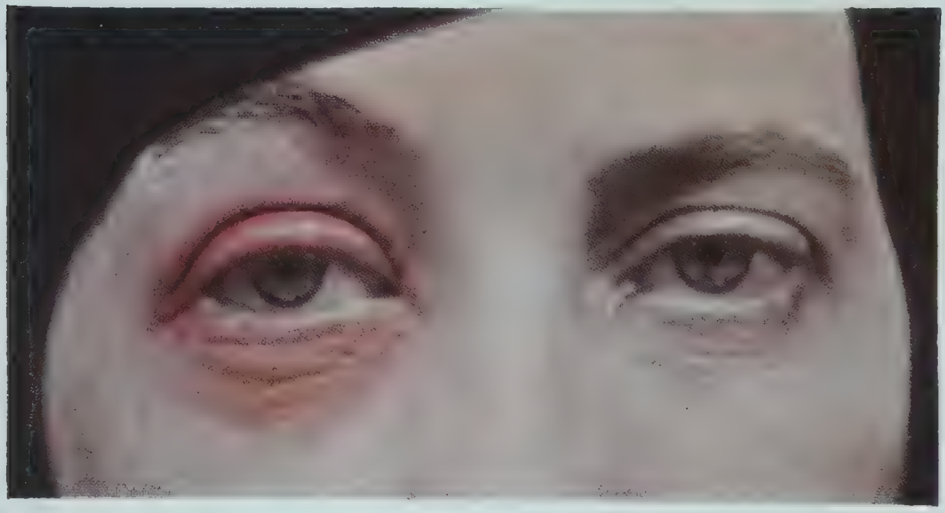

Fig. 20.—Case 3. C.G. Intrinsic allergic dermatitis due to tomato. Identical lesion reproduced by tomato externally applied.

This case had been diagnosed as "eczema" on several occasions over the previous four years. It is particularly interesting in that it demonstrates the strict localization of the sensitized area. General patch testing was negative, but when the allergen was applied to the sensitized cells of the eyelid a typical response was obtained. It illustrates not only one of the difficulties in testing, but also the fact that the food allergen whether externally applied or ingested can produce the same dermatitis.

Case 4. N.S., a woman, aged fifty-three, had no history of familial or past or present personal allergy other than the skin lesion. For nine years she had had a patchy dermatitis over the body which appeared and disappeared in various areas, but she had never been wholly free. Under general and local care and with improved diet and vitamin therapy she was almost free and had no acute attacks for six months. Then suddenly she had an acute general eruption which required her hospitalization. The environment had been the same. The only different food taken prior to this episode was cantaloupe. A few weeks after she had recovered from this attack she again ate cantaloupe, and the second day following she again had an acute general oozing eruption and abdominal cramps. Patch tests with fresh cantaloupe were done about ten days later and were positive. The intradermal test gave no immediate urticarial wheal. Tea was also under suspicion. The patch test to it was positive, and the use of tea was followed after several days by a general eruption. The intradermal test to tea was negative. These were not the only offending food allergens, for there have been attacks not attributable to cantaloupe or tea, but no other patch tests have been positive.

This case, diagnosed as neurodermatitis, shows the difficulty of classifying or pigeonholing many of these cases on clinical grounds. Here again was a patient, like the previous one, devoid of family or personal history of allergy, with no external contacts as proven allergens, and yet susceptible to diagnosis, at least in part, by patch test with food substances when a clue as to the probable allergen was obtained by the history.

One of the difficulties in the discussion of the immunologic relationship of intrinsic and extrinsic dermatitis lies in the fact that an etiologic diagnosis is rarely made in the latter group. My observation has been that the clinical diagnosis of external contact dermatitis is made when a positive patch test has been obtained to some substance with which the patient has known external contact, but when all possibilities have been exhausted and no positive patch tests with such substances are secured, then the diagnosis of "eczema," "neurodermatitis" or "atopic dermatitis" is made, the last especially when any suggestion of an allergy may be uncovered in patients or their antecedents. This may satisfy the patient or physician, but is hardly sound. However, it does indicate the clinical identity of the two conditions.

The point I wish to make is that *immunologically speaking there is no discoverable difference between allergic dermatitis arising from external contact (extrinsic) and that due to other causes such as foods, drugs and bacterial products (intrinsic)*. Both may occur from infancy to old age in patients who have or do not have evidence of other allergies. This is in accord with Peck's[13] belief, but is not in agreement with Sulzberger[11] or Coca,[14] who feel that the patch test is suitable for contact dermatitis only, but not for the lesion which they term "atopic dermatitis."

I believe that the difficulty of an etiologic diagnosis in the intrinsic dermatitis of infants and adults is largely due to the fact that we have not yet learned what materials to use for patch tests. A clinical observation by Mason[15] supports this belief. In his case an infant on breast milk alone developed a severe generalized skin lesion. It was discovered that the mother was eating fresh rhubarb daily and in large amounts. This was stopped and the baby made a rapid and complete recovery while continuing breast feeding. All other food and environmental factors were unchanged. This raises a point that is not often taken into account, namely that when one speaks of dermatitis due to milk, either human, cow, or goat, even in clinically well proven cases, one is apt to lose sight of the fact that the dermatitis-producing factor may be a fat- or water-soluble substance derived from the diet of the female producing the milk, and not an allergy to the milk proteins per se, or any regular milk constituent.

Summary. Evidence exists for the allergic basis of certain exudative lesions of the skin. These reactions occur to substances that in general are not primarily irritative. Evidence is also present for my belief that allergens producing only wheal reactions do not cause dermatitis and therefore skin testing for immediate wheal reactions is not a correct procedure for an etiologic diagnosis of these exudative skin lesions.

Any allergen, however, which on patch test produces the delayed exudative lesion of the epidermis may on proper contact, externally or internally, be a cause of dermatitis since the test has reproduced the clinical lesion. In other words, the immunologic bases of the wheal reaction and the dermatitic reaction are not the same and the immediate wheal reaction can never be used as an index for a dermatitic lesion.

Finally there is evidence indicating an identity of the immunologic basis for extrinsic allergic dermatitis due to external contactants and that due to other allergens provocative of intrinsic allergic dermatitis, the so-called infantile eczema (atopic dermatitis).

The nomenclature suggested to indicate the immunologic identity of allergic dermatitis of external and internal origin is (*a*) intrinsic to indicate the infantile type or atopic dermatitis and (*b*) extrinsic to indicate the external eczematoid contact dermatitis.

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14. *Allergic Dermatitis: Intrinsic (Infantile Eczema—Atopic Dermatitis)*

ROBERT A. COOKE

IN THE allergy known as intrinsic dermatitis the lesion of reaction occurs when the sensitized cells of the derma, or corium, come in contact with an allergen conveyed to them through the blood or lymph. It may be acute and recurring, or chronic with occasional exacerbations. In infancy it is frequently a short, self-limited disease.

Many of the cases have a familial or personal background of allergy, though this is not necessary. The condition frequently, but not always, occurs in persons who have other allergies as hay fever, asthma or urticaria, which are etiologically and immunologically unrelated to the skin lesion. Many of the cases begin during infancy and childhood, but symptoms may develop at any age and even in the elderly.

Etiology

The discussion of causes is difficult for properly verified etiologic diagnoses of the allergens are made with relative infrequency. The specific irritants are brought to the sensitized cells of the skin by blood or lymph; in other words, they are absorbed from the intestinal tract or are parenterally introduced or derived from foci or areas of infection. This means that in reality one is dealing with substances absorbed through inhalation, ingestion, injection and infection; in other words they are air-borne substances, foods, drugs and bacteria or their products.

Accessory or contributing factors such as age, season, temperature, skin texture, psychic and endocrine disturbances may play a part, but only a secondary role, for such conditions do not directly initiate sensitization nor provide the allergens which are the two responsible factors in the creation of an allergic lesion.

Air-borne Substances. Peck and Salomon[1] have called attention to the importance of air-borne allergens as causative factors in eczema of infants and children. They claim that these factors are more important than foods, that they act by contact rather than by absorption after inhalation, that patch tests are valuable and scratch tests are of little value. Hill[2] after repeating this work "disagrees with them in their method of testing and with most of their conclusions." He found no positive reactions in twenty-five patients patch-tested with environmental allergens. However, on the basis of positive scratch tests with air-borne environmental allergens. Hill[2] concludes that "after the second year they are as important as foods."

My own experience with these inhalant allergens is not in entire accord with that of Peck and Salomon[1] or that of Hill.[2] While I agree that a large percentage of infants and children with dermatitic skin lesions give positive scratch or intradermal tests (immediate-wheal type) to inhalant allergens, it has not been possible in my cases to produce a dermatitic skin lesion with patch tests of such substances. The positive test, intradermal or scratch, merely indicates allergies of the wheal-reacting type then existing or to be developed later (Chapter 2). Patch tests with these substances have been uniformly negative in my patients, even when the original substances and not their water-soluble components have been applied. My present feeling is that air-borne substances acting after absorption by inhalation are not factors in the causation of dermatitic lesions as contended by Sulzberger and Vaughan[3] in experiments with silk, but as external contact allergens they may occasionally produce typical dermatitis, as in the cases of seasonal rash caused by ragweed oil as reported by Bengtsson[4] and by Gay and Ketron,[5] and by timothy pollen protein as recorded by the Mitchells,[6] and other cases such as those of Feinberg.[7]

Foods and Drugs. Hill[8] has said, "Sensitivity to the protein of cow's milk is probably the most important single cause of atopic dermatitis (eczema) in infancy." This opinion is apparently based on the immediate wheal reaction, for he adds, "A positive scratch test almost always indicates clinical sensitivity," meaning presumably "eczema" (allergic dermatitis), the subject of his paper. He also places wheat and other cereals high on the list of causes, with vegetables, orange and fish oil of much less importance. As to egg white he states, "Most atopic infants react to egg white. . . .egg is of little importance as a causative factor in the atopic dermatitis of young infants since most of them have never eaten it and those who have, have had it removed from the diet as soon as the dermatitis started, usually without any benefit whatever." In general this is the consensus among pediatricians and allergists, but at best the results of diet changes have been poor and disappointing. Hill[8] sums it all up very well when he says, "I have seen nothing in the literature, including my own contributions, which leads me to believe that anyone really understands infantile eczema or that there is now any method of treatment, dietetic or otherwise, that is consistently and entirely satisfactory." With this I heartily agree. What is needed is more light and a new approach, and my personal opinion is that the work has been hampered by a belief in the diagnostic significance of the immediate wheal type skin test, which I have attempted to show and which I believe has no significance in dermatitis.

This, however, is not to deny that foods and food factors may be of importance. I have cited two cases in Chapter 13 (pp. 244–245) showing sensitivity clinically and by patch test, one to cantaloupe and tea, and the other to tomato. In these proven cases there is little reason to believe that this was a protein reaction. In fact, my experience leads me to regard proteins as such, even including those of milk, as very minor factors, for in spite of our many trials by careful feeding experiments and patch tests only once has a protein substance given a positive patch test reaction, and this was not a food. The following case report describes this instance:

Case 1. D.W., a man aged thirty, had autumnal hay fever for three years and was then treated for two years with reasonably satisfactory results and no general or undue local reactions to the pollen extract. His maximum dose was 7000 protein nitrogen units of ragweed extract. The next year, after a lapse of treatment of nine months, he was tested intradermally with ragweed pollen extracts of the usual strengths (10, 100 and 1000 protein nitrogen units per milliliter). He had the typical immediate local wheal reactions as in previous years. Twenty-four hours later there was considerable edema and vesiculation about the test sites. This reaction increased and covered the arm from shoulder to wrist and persisted for four days. It was a dermatitis, not an angioedema. On account of the extreme edema it looked like a severe sumac poisoning. The patient did not have any history of seasonal dermatitis. Patch tests with regular ragweed extract and purified ragweed pollen albumin produced a local dermatitis beginning in twenty-four to thirty-six hours, and lasting five to six days (Fig. 21). Patch tests with pollen and plant phenols (ether-soluble substance) were negative.

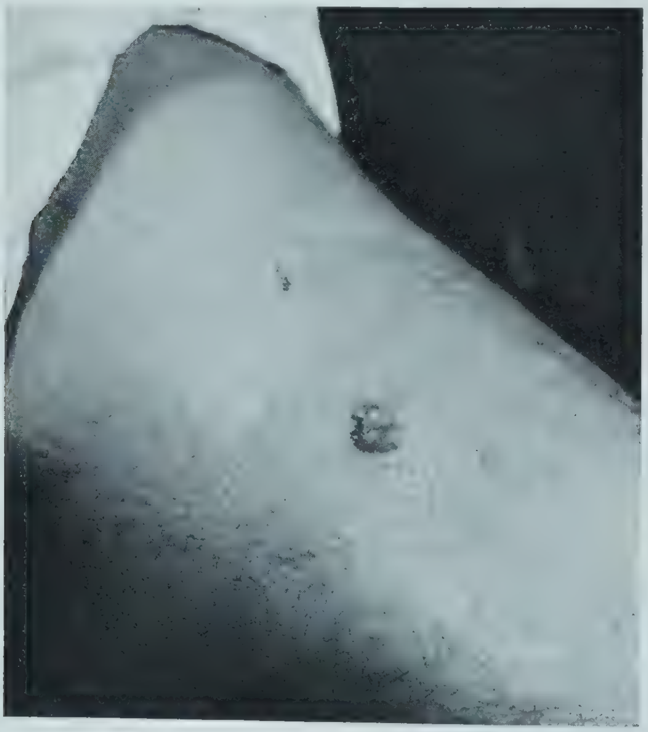

Fig. 21.—Case 1. D.W. Dermatitic reaction to a patch test with ragweed pollen albumin.

A similar case was reported by the Mitchells.[6] Their patient had seasonal dermatitis due to the albumin fraction of timothy pollen, but no hay fever. Such cases support the idea that proteins can and do produce a positive delayed dermatitic test lesion if and when they are a real cause of dermatitis.

However, I cannot speak definitely as to the importance of foods in causing dermatitis, for our group of cases is small and our studies have led to negative rather than positive results. As a result of our observation on patients under hospital care many suspected foods, such as milk, wheat, egg (if it could be eaten), have been proved *not* to be causes of dermatitis. We have never had the satisfaction of proving any food to be a cause in the infants under our observation, though I see no reason why it should not be so. Perhaps further study will show that the food allergens inducing intrinsic dermatitis are of the same general order and chemical constitution as those now known to cause extrinsic dermatitis, namely the vegetable dyes, resins, oils and complex organic and inorganic substances other than protein.

Drugs and biologic products taken by mouth or injected, as well as externally applied, are important. In this list are arsenic, mercury, iodine, the sulfa compounds, phenolphthalein, coal tar products, salicylates, the barbiturates, bromides and chloral, ephedrine, penicillin, liver extract and vitamin preparations, as well as local anesthetics such as procaine, anesthesin, novocain and pontocaine, to name but a few of the more conspicuous ones. It makes no difference whether the drugs are given internally or parenterally, or are used by external application as is frequently done with the mercurials, iodine and the sulfonamides, for in the sensitized patient the lesion results when they are taken into the system by any route. It is absorption and eventual contact with sensitized cells that count, not the gate through which the allergen enters.

The following case is a typical example:

Case 2. A.G., a housewife aged thirty-nine, had a general itching and oozing eruption over the entire body, beginning one week before she came in for treatment. She had a history of a similar attack about six months before. Each time she had had a "cold" and had taken certain pills. A patch test with the pill substance, supposedly acetylsalicylate, was positive, but the patch test with pure acetylsalicylic acid was negative, while a test with methylsalicylate was positive (Fig. 22). A year later a recurrence, with lesions only in the mouth, was found to be due to the local application of oil of wintergreen in toothpaste.

Bacteria and Fungi. It is well recognized that bacteria and fungi may find a fertile soil in lesions of the skin, especially those in which there is an abraded exuding surface. The frequency of streptococcal pyoderma in dermatitis of children has been stressed by Boisvert and Powers.[9] Such secondary infections require care and special local treatment, for they certainly aggravate the dermatitis. But we are concerned with dermatitic lesions actually caused by bacteria or fungi acting as allergens. This means that the cells of the skin are not actually invaded by the exciting organisms, but that the sensitized cells are reacting to bacterial substances or products absorbed from distant foci.

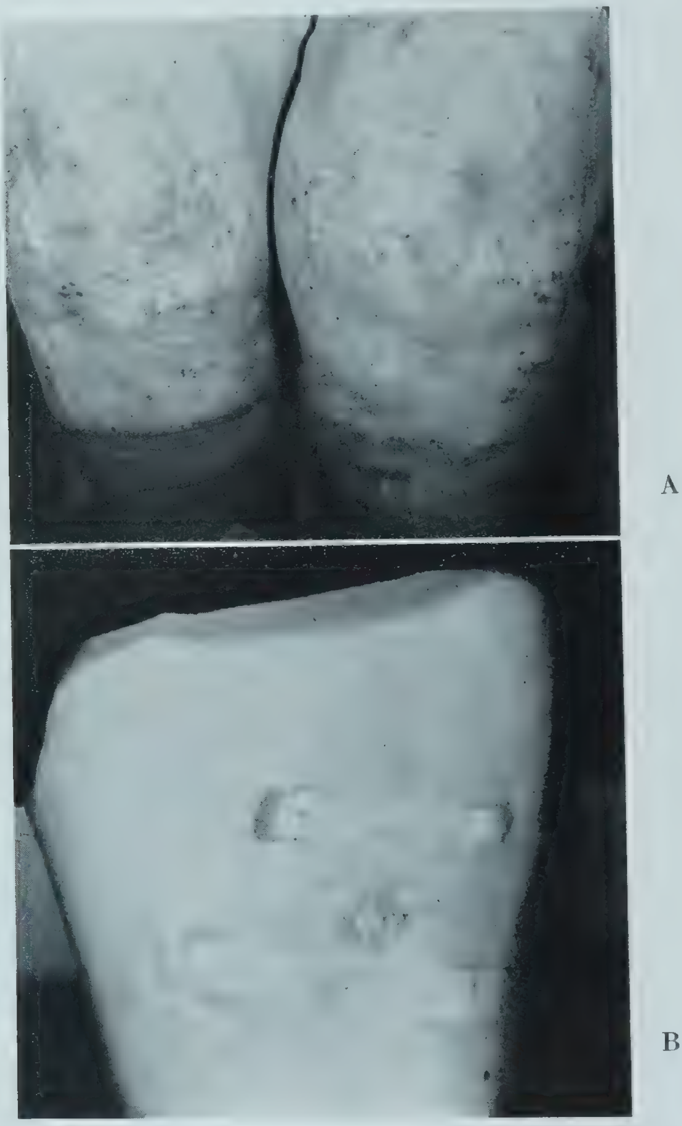

Fig. 22.—Case 2. A.G. *A*, Intrinsic allergic dermatitis following methyl salicylate by mouth. *B*, Positive patch test with methyl salicylate.

The following case to my mind represents a typical and well proven example of allergy to the bacteria from a focal area expressing itself clinically as an acute recurring intrinsic dermatitis.

Case 3. A.V., a woman, aged forty-nine, had a history of three attacks of acute swelling and exudative eruption on the face and neck (Fig. 23). These appeared a few days after an acute upper respiratory infection and lasted ten to fourteen days. The first attack was attributed to a "cold" remedy, so no medicine was used before the last two attacks. On operation there was found a dentigerous cyst of the edentulous upper right bicuspid area and a cyst of the right antrum. A hemolytic strain of Staphylococcus albus was cultured from the tissue from both operated areas. Later, and on three separate occasions, when the skin was normal, an acute dermatitis of the face and neck appeared thirty-six hours after an injection of 0.05 ml. of a 0.1 per cent suspension of the autogenous vaccine made from the staphylococcus recovered from the tissue.

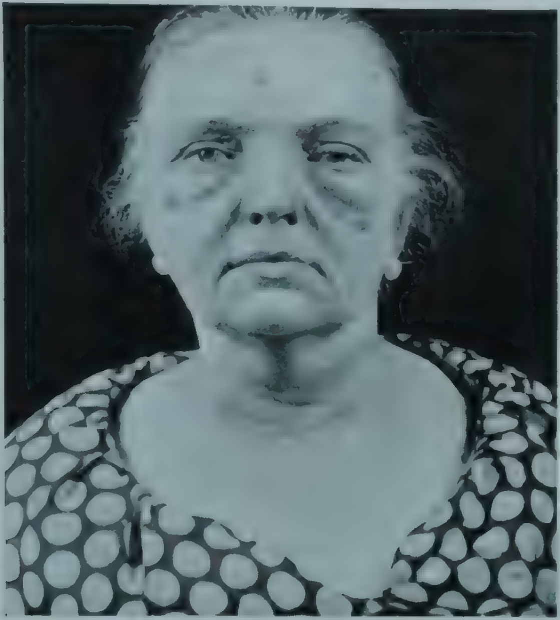

Fig. 23.—Case 3. A.V. Intrinsic allergic dermatitis. This acute lesion was reproduced by an autogenous vaccine injection.

Another illustration is seen in the following case:

Case 4. F.L., a woman forty-nine years of age, fifteen months before the first consultation at the clinic developed an eruption about the rectum, vulva, groins and thighs. This was a fine measly rash with intense itching and oozing, and the first attack lasted ten weeks. Six months later a rash broke out over the entire body, and partially cleared after two months' time. With the next exacerbation she sought relief at the clinic. The history disclosed an unusual story of family hypertension. She herself had a systolic pressure of 160, diastolic 100. There was no history of allergy. A recurring vaginal ulcer had been present over the past four years. The patient's general condition was good. The skin showed an acute vesicular eruption over the body, face and extremities (Fig. 24). Examination of the upper respiratory tract showed no infection. The jaws were edentulous. Gynecologic examination disclosed a large abscess of the left Bartholin gland. Cultures taken at the time this was operated upon yielded a beta hemolytic streptococcus and hemolytic Staphylococcus aureus.

Within one month after the operation the skin was normal except for a fading pigmentation, and has continued to be so after a year. The Wassermann reaction was negative. The urine was normal. A blood eosinophilia of 10 per cent on admission had returned to normal four months after operation.

While Case 4 cannot be classed as a proven case, the rapid subsidence of the skin lesion after operation and the continued freedom from all symptoms, together with the return of the eosinophil count to normal, make the diagnosis of intrinsic dermatitis secondary to focal infection satisfactory but not conclusive.

As a result of these and similar cases I have been much interested in the role of foci of infection as allergen sources in the production of dermatitis in infants and children as well as in adults. The difficulty lies in establishing definite proof, and a confirmatory result such as that seen in Case 3 is not often or easily obtained. One clue may be gained by eliciting a history of acute infection, usually of the respiratory tract, prior to a cutaneous exacerbation. The organisms most frequently found in the foci in these cases are: beta hemolytic streptococcus, pneumococcus and hemolytic staphylococcus. I do not believe that general or localized bacterial infections as sources of allergens active in allergic dermatitis have been generally appreciated or explored as fully as they deserve to be.

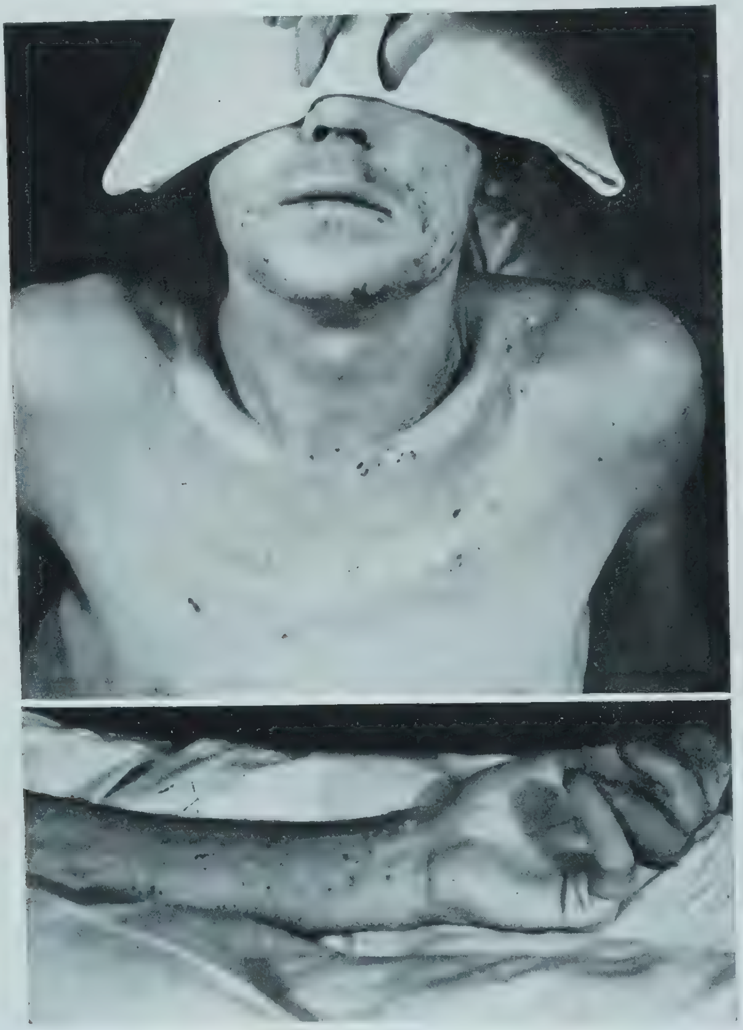

Fig. 24.—Case 4. F.L. Intrinsic allergic dermatitis disseminated.

That focal fungus infection may give rise to a general cutaneous allergic reaction has long been recognized. The cases are not rare in adults, but in the infants under my care this type of lesion has played an insignificant role.

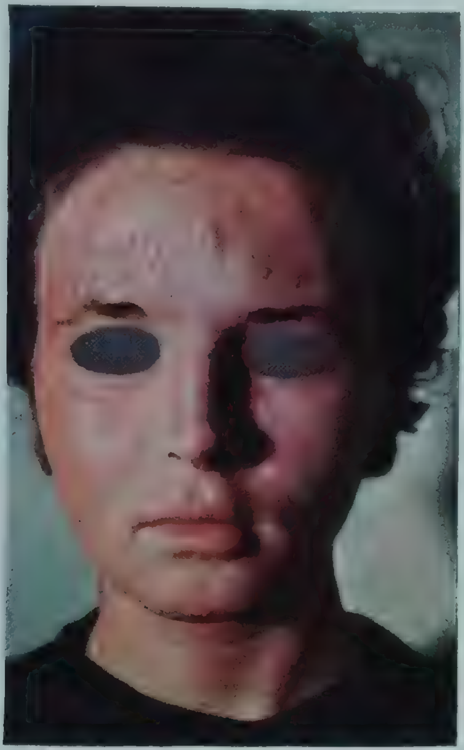

Fig. 25.—A case of intrinsic allergic dermatitis (infective) during an exacerbation following an acute upper respiratory infection.

Diagnosis

Definite causes of allergic dermatitis discovered and proved are, except in that due to external contacts, *relatively rare*. There are available two diagnostic approaches—skin tests and clinical observations—to support the clues obtained by a careful and detailed history.

Skin Tests. I have not found that scratch or intradermal tests, even though giving the immediate wheal reaction, have any diagnostic significance in allergic dermatitis (p. 238). They may indicate the cause of other existing allergies of the edema type, as asthma or allergic coryza, or they may foretell the allergies to come. Thus they have some value in the management of the patient but no value in the management of the existing skin lesion.

The delayed intradermal reactions of an inflammatory type with trichophytin and oidiomycin definitely signify allergy and may indicate a cause if an existing focus is discovered. They are similar to the tuberculin reaction. However, this is not the case with the bacterial vaccines, filtrates, extracts or toxins as now prepared. Delayed reactions on intradermal test with such preparations are common in children and adults, but I have not been able to correlate them with the skin lesions of allergic dermatitis.

Delayed exudative type reactions have been produced in a few instances with very superficial intradermal injections. I recall a patient with dermatitis due to pontocaine in whom I obtained such a reaction, and others who reacted similarly to poison ivy extract. But the intradermal method of testing is not as satisfactory as patch testing.

Patch Tests. With these tests we seek to reproduce in miniature the general histologic characteristics of the lesions under study. Difficulty in applying patches may result from the condition of the skin in the patient with extrinsic dermatitis. In the acute disseminated lesion no patches can be applied unless there is sufficient normal skin. On lichenified skin absorption is unreliable, and in any case adhesive plasters are apt to produce irritation or their specific lesions.

A second possible stumbling block is encountered, as exemplified by Case 3, Chapter 13 (p. 244), in which there happened to be a localized area of sensitivity. Where the clinical lesion has been restricted one should apply the test to or near the area of the previous lesion.

ALLERGENS FOR PATCH TESTS. Just as under etiology the allergens are divided into air-borne substances, foods, drugs and bacteria and their products, so may the same general classification be followed for the allergens to be used.

In view of the existing inadequacy of our information it is wise to do all patch tests with the suspected substance, regardless of the class to which it belongs (that is air-borne, ingested, etc.), in the form in which contact is made and preferably with the very substance used by the patient. This is illustrated by our experience with Case 2 (p. 252), when a supposed aspirin pill was found to contain a reacting amount of methylsalicylate, while the patch test with the pure acetylsalicylate was negative. Likewise, extracts of foods might well be unsatisfactory if a watery extract is used when the actual allergen is ether- or alcohol-soluble. This problem is much more complicated with the bacterial allergens, for as yet we do not know whether patch tests are feasible or not with any type of this material. Convincing evidence is obtained only with a symptomatic reaction to autogenous vaccines (Case 3, p. 253).

(1) Air-borne Substances. These really should be classified as allergens of external contact type dermatitis, although they have been considered by some to act after absorption in the respiratory tract. The possible substances are many on account of the multiplicity of domiciliary, occupational and casual contacts. The patient's history should afford

suggestions. When the dermatitis is seasonal, the allergens may be pollens or fungi. If continuous at home, they may be dusts or feathers, as suggested by Peck and Salomon,[1] and if the lesion is active when at work and disappears when the patient takes a few weeks' vacation, then contacts at the shop or factory should be investigated. Actually, in my experience air-borne substances are of slight or no importance in intrinsic dermatitis.

(2) Foods. Tests with foods regularly or frequently eaten may be tried, as well as with foods occasionally eaten if indicated by the history. At present it is safer to patch-test with foods in the form in which they have been eaten. The history can be extremely important in these cases.

(3) Drugs and Biologicals. Those used for home medication as well as those being taken under medical advice are certainly possibilities, and all should be tried. The test should be made with the drug in the exact form in which it is taken.

(4) Bacteria. Nothing is known at this time of any procedure for testing with bacteria or their products by patch technic.

TECHNIC OF PATCH TESTING for foods and drugs and biological products is exactly the same as that for the external contactants (see p. 266).

Clinical Study. In all cases the clues to a solution of the problem may be found in a careful clinical study. This means a very detailed *history* of the circumstances under which the skin lesion began and those attending its exacerbations, as well as the location of the lesions and seasonal variations. The occupational and home contacts must be carefully investigated as a matter of differential diagnosis. The diet, drugs or other medicaments used, occurrence of other disease, especially infections, may all be significant. The *physical examination* is important, especially with regard to foci of infection. A differential blood count should be taken. A blood eosinophilia above 5 per cent is common in all dermatitis cases except those due to external contact.

Having made a careful study of the patient and applied whatever patch tests seem indicated, it is then necessary in the event of negative results to resort to the sound clinical procedure of *trial and error*, in this case avoidance and use.

Air-borne Substances. These must at least be given consideration as a part of the differential and etiologic diagnosis, especially in those cases in which external contacts might be a cause. A rapid and unusual improvement after complete environmental change as from home to an air-conditioned hospital room in the summer months is highly suggestive. Other contactants as cosmetics, soaps and fabrics must be eliminated also.

Food and Drugs. If a clue to food allergens is not secured from the history one may utilize dietetic restrictions. This is difficult and often inconclusive. My own preference is for a simple high protein non-resinous diet as in Diet No. 1, including milk, eggs, meats, butter, cream, cheese and sugar. This diet is used in all cases except in infants who cannot eat a certain food on account of an allergy of the immediate wheal type. Or one may, in adults, use one of the preparations of the essential amino acids, such as Amigen (Meade Johnson). This is presumably nonantigenic and must be given intravenously. It is available in 5 per cent glucose and 2 liters a day will usually suffice to maintain nitrogen balance. As it takes about four hours per liter for intravenous drip this is well tolerated twice daily (twenty-four hours), as from 8 A.M. to noon and from 6 to 10 P.M. Nothing but water in unlimited amounts is given by mouth. This procedure may be used for three or four days without undue hardship. Attempts are being made to provide a palatable preparation for oral use.

ANIMAL PROTEIN TEST DIET—No. 1*

Soup	Meat soups only. No vegetable or cereal additions.
Meat	Any kind, including bacon. Gravy with arrowroot but no flour may be used.
Poultry	Any kind.
Fish and shellfish	Any kind.
Milk or buttermilk	As desired.
Cream	As desired.
Eggs	One or two per day.
Cheese	As desired.
Fruit	None.
Vegetables	None.
Salads	None.
Cereals	Arrowroot starch only.
Bread	None.
Fat, butter, or meat fat	Lard, bacon fat, chicken fat, or drippings. No vegetable fat or oils.
Desserts	Arrowroot pudding (caramel), junket (vanilla, caramel). Butterscotch, baked custard, caramel custard. Gelatins.
Beverages	Tea. Milk. No fruit juice or coffee.
Condiments	Salt allowed, and small amount of pepper. No chili sauce, catsup, etc.
Sweets	None except sugar.
Nuts	None.

SAMPLE MENU

Breakfast	*Dinner*	*Supper*
Grilled ham	Beef broth	Chicken soup thickened with arrowroot
Egg	Steak or fish	Melted cheese on poached egg
Butter	Baked custard	Bacon
Tea or milk	Buttermilk	Vanilla junket
Cream	Blanc mange	Tea or milk
Sugar		Arrowroot crackers and butter
Arrowroot crackers		

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* Any food to which the patient has a known and definite sensitivity must of course be omitted.

INFANTS. A sensitization to egg with an immediate edema reaction is common in infants even though it is not a factor in dermatitis. Egg and often chicken and chicken broth must be omitted entirely from the diet, but this, while creating difficulties, is not an insuperable obstacle.

The management of these patients is oftentimes difficult. The easiest procedure is to start the infant on milk, preferably evaporated or well boiled, as Ratner[10] has suggested to denature the protein.

There are several proprietary preparations of the ten essential amino acids usually derived from casein and now commercially available. These are obtained either by enzyme or acid digestion. Although extremely disagreeable by taste and smell for older children and adults, Hill[11] has shown that infants may be maintained in proper protein balance for long periods of time by oral amino acid therapy.

VEGETARIAN TEST DIET—No. 2*

Soup	Vegetable soup—made without meat stock.
Meat	None.
Milk	None.
Cream	None.
Eggs	None.
Cheese	None.
Fruit	Any fruit or fruit juice—use freely.
Vegetables	All kinds—use freely.
Salads	All kinds.
Salad dressing	May have French dressing, olive oil or vegetable oil substitutes. No mayonnaise or dressing containing eggs.
Cereals	All kinds—including flour, cornstarch, arrowroot sauce.
Breads	All kinds.
Fat	Crisco or Spry as butter substitute.
Desserts	Fruit juice thickened with cornstarch, fruit cup, fruit pie made with Crisco or Spry, tapioca, fruit ices (no egg white, no gelatin).
Beverages	Tea, one cup coffee only, fruit juices, soy bean milk.
Salt	In moderation only.
Sweets	May have reasonable amount of jam, jellies, marmalade, honey or nuts.

SAMPLE MENU

Breakfast	*Dinner*	*Supper*
Stewed prunes	Vegetable broth	Fruit juice cocktail
Wheatena with fruit juice or syrup	Cauliflower (sauce of thickened cauliflower water)	Peas
Whole wheat toast—butter substitute	Spinach—butter substitute	Carrots
Jelly or marmalade	Baked potato	Mashed potatoes (no milk)
Coffee or fruit juice	Tomato salad (French dressing)	Nut and pear salad (French dressing)
Sugar	Whole wheat bread—butter substitute.	Whole wheat bread—butter substitute
	Oatmeal cookies	Orange ice
	Clear tea—sugar	Tea—sugar

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* See footnote, Diet No. 1.

If milk is first used and one can be satisfied that it does not increase dermatitis or produce the edema reactions with vomiting and asthma, other foods can then be added but always in sufficient amounts so that a dermatitis may result and can be recognized; for instance orange juice should be used in amounts of 4 to 6 ounces a day for one week unless interrupted by exacerbations. When this happens the orange juice is omitted and milk is continued until the lesion has subsided. At this stage one either makes a new trial with orange juice or makes a similar attempt with one of the leafy vegetables like spinach in goodly amounts for weekly periods. Before being convinced of the allergenic activity of any food one must always try it under proper conditions at least three times, and if it is a true allergen the same result should follow.

OLDER CHILDREN AND ADULTS. The edema reactions with foods are relatively so uncommon in this age group that the problem is much less difficult.

If a diet such as No. 1 is successful, and it has often been, then other foods by classes, as citrus fruits, root vegetables, then leafy vegetables are added. If unsuccessful, and again it has been, then a complete reversal is made and fruits and green vegetables are used freely as in Diet No. 2.

In all such therapeutic trials no diet must be prolonged beyond two weeks without proper attention to proteins, vitamins and minerals to prevent serious nutritional disturbances. In any case, if a diet succeeds once it must always succeed, and if a food is suspected it must always regularly reproduce the lesion under identical conditions on repeated trials.

All drugs, whether suspected or not, used externally or internally, must be avoided completely to simplify the problem. Proof of their activity may be secured at a later date when their use should precipitate a reasonably prompt return of the lesion.

Focal Infection. If focal infection is a suspected cause, the focus of infection should be removed at the earliest opportunity. In infants who have a focal infection in tonsils and adenoids, operative removal may be performed as early as twenty months of age, providing conditions are right. Such cases do not give opportunity for establishing proof except by reproducing the lesion with vaccine injections, as in Case 3 (p. 253). Satisfactory and continued improvement after the operation will satisfy patients or parents, if not a scientifically minded physician.

Treatment

First to be emphasized in the general management of allergic dermatitis is the importance of *never* giving or allowing to be given any vaccination against smallpox to any child or adult with an existing dermatitis, and *never* permitting the vaccination of a child or an adult when there is an existing dermatitis in any member of the household. Not long ago I saw a woman who had had dermatitis since infancy. Six months previously she nearly died from vaccinia, having contracted the disease from her newly vaccinated baby.

The treatment of dermatitis is directed against the cause and to the relief of symptoms (Chapter 17).

Etiologic Therapy. The principle of etiologic therapy is tersely expressed as one of avoidance of the cause. This of course assumes that the specific cause, or at least its source, has been determined.

(1) *Dermatitis Due to Ingested Foods and Drugs.* Avoidance is the most practical procedure. For this reason it is important that the cause be found if possible, for prolonged dietetic restrictions should not be imposed without substantial proof of the necessity. If an essential food is found to be a cause, substitutes must be suggested. With most foods and with drugs avoidance is easily carried out. In my experience so far foods have been implicated in a very small percentage of the cases.

(2) *Dermatitis Due to Infections.* Those infections that are acute and recurring usually involve the respiratory tract and may be avoided or prevented by the usual prophylactic measures against respiratory infections.

With infections of a chronic type giving rise to persistent dermatitis with occasional exacerbations, the source or focus must be eliminated. In infants and young children these primary foci are found in the tonsils and adenoids; in older children and adults, teeth and sinuses may also be the seat of trouble. But a focus may exist anywhere and a careful search must be made. Removal of foci is indicated in all cases in which age and general physical conditions do not offer contraindications. (See treatment of foci, under Asthma, p. 152.) If removal of foci is not possible or is contraindicated, treatment with antibiotics and vaccines (autogenous if possible) is indicated.

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15. *Allergic Dermatitis: Extrinsic (External Contact Type Dermatitis)*

LOUIS SCHWARTZ*

Definition

Before I can discuss this subject I must clearly define what I mean by extrinsic or allergic contact dermatitis. Irritant substances which act on the skin may be divided into two types: (1) primary irritants; (2) sensitizers.

A *primary cutaneous irritant* is an agent which will cause dermatitis by direct action on the skin, at the site of contact only, if it is permitted to act in sufficient intensity or quantity for a sufficient time. A primary cutaneous irritant forms a chemical combination with the skin, or abstracts one or more of the essential ingredients of the skin, such as the moisture or the fatty matter.

A *cutaneous sensitizer* is an agent which does not necessarily cause demonstrable cutaneous changes on first contact, but may effect such specific changes in the whole skin that after five to seven days or more, further contact at the original site or any other portion of the skin will cause dermatitis. It is this type of dermatitis which is here known as allergic extrinsic or allergic contact dermatitis.

Primary irritants may also be sensitizers; for instance, formaldehyde, alkaline bichromates, phenols and phenyl mercuric compounds. A primary irritation dermatitis caused by strong concentrations or large quantities of these substances may also cause such changes in the skin that contact thereafter with low concentrations or small quantities that would not before have affected the skin now cause dermatitis.

We must also make a distinction between response of the skin to the action of chemicals because of anatomic faults or physiologic dysfunction, and the hypersensitivity of the skin which we call allergy. Allergy is a phenomenon of altered reaction initiated by first contact with a substance and manifested after an interval (period of incubation) upon further contact with the original or an identical substance.

People with thin layers of epithelium are more susceptible to the action of primary irritants than those with thick layers of epithelium. On the same person areas of the skin having thin layers of epithelium, such as the eyelid, are more susceptible to the action of skin irritants than areas of the skin with thicker layers, such as the back. People with inactive sweat glands and dry skin are more susceptible to the action of dehydrating chemicals than those with active sweat glands and moist skin.

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Adopting this conception of allergic contact dermatitis, the large majority of cases of occupational dermatitis are not of an allergic nature. They are mostly caused by primary irritants acting on workers who have anatomic or physiologic defects of the skin, or on normal workers who have excessive contact with the chemicals, either because of the nature of the work or because they fail to use such proper protective methods as clean protective clothing and frequent cleansing of the skin. This does not mean that anatomic defects of the skin, physiologic dysfunction of the glands of the skin, prolonged contact with the chemical caused by uncleanliness, or rubbing the chemical into the skin at sites of friction, may not also be predisposing causes of allergic contact dermatitis. Such conditions will permit a cutaneous sensitizer to come in more intimate contact with the skin, and thus enable it to more readily produce allergic contact dermatitis.

For a discussion of the allergic basis and the immunologic mechanism of extrinsic allergic dermatitis, see Chapter 13.

Occupational Allergic Contact Dermatitis

Diagnosis. It is of importance to determine, first, whether a given case of dermatitis is actually occupational in origin, and second, whether it is caused by a primary irritant or by allergy, because on this latter fact may depend the installation of costly preventive measures, and on it may also depend the award of compensation. It is easier to install protective measures against primary skin irritants than it is against sensitizers, and compensation is more readily awarded for dermatitis caused by a primary irritant (it may be classed as an accident) than for dermatitis in which the peculiar idiosyncracy of the patient is the major cause. We have noted instances where there occurred only a few cases of dermatitis among a group of workers and therefore it seemed probable that these were caused by allergy, but upon closer examination it was found that the workers affected were either less cleanly than those who were not affected and therefore had more contact with the chemicals involved, or they had breaks in the defense mechanism of the skin which permitted them to have more intimate contact with the chemicals than did the other workers. Patch tests with the chemicals elicited no greater percentage of positive reactions among those having dermatitis from some other cause than those not having dermatitis. Therefore, we concluded that the dermatitis was not caused by allergy, but that either the chemicals were allowed to remain on the skin for longer periods of time, or they more easily penetrated the thin or injured skin of those affected than the normal skin of those who were not affected.

The following points must be considered in making a diagnosis of allergic occupational dermatitis:

1. *History.* Under this heading come a number of factors:

(*a*) It must be shown that the dermatitis from which the patient suffers was not present at any time before he entered on the occupation.

(*b*) Knowledge of the skin-sensitizing action of the chemicals handled by the worker may lead to the suspicion that the dermatitis is of an allergic nature. We know that workers with nitro-, chloro-, and many other organic compounds, and with plants, often become sensitized to their action. We must also be sure that there has been no exposure to primary skin irritants although it must be remembered that specific sensitization can follow a dermatitis or burn caused by a primary irritant.

(*c*) It must also be shown that the dermatitis developed after a period of incubation of at least seven days after first exposure to the sensitizing substance.

(*d*) An investigation in the factory should show that most of the other workers similarly exposed are not affected.

There are seeming exceptions to the length of the period of incubation. For instance, if a worker has worked in another factory where he was exposed to the same chemical but did not develop dermatitis, nevertheless he may have become sensitized at that factory and then developed his dermatitis very shortly after an apparent first exposure in the second factory. This does not shorten the real period of incubation. Then again, a worker may develop a local burn or dermatitis the first day that he handles a primary skin irritant. This may sensitize his entire skin surface to such dilutions of it as would not affect the normal skin. In such case, however, the sensitization to non-irritant dilutions comes on after a period of incubation of seven days or more, and may be manifested by a subsequent generalized dermatitis. In such instances the majority of workers exposed to the primary irritant will develop dermatitis shortly after exposure, but only a small percentage of them will subsequently become sensitized to dilute solutions of the irritant.

2. *Site of Eruption.* While the eruption in an allergic occupational dermatitis usually begins on the parts visibly exposed, just as it does in dermatitis caused by a primary skin irritant, parts of the body which are covered by the clothing and but little exposed may also become affected, because the whole skin is sensitized and it takes the presence of only a small amount of the allergen to bring on an inflammatory reaction. Such small amounts of the chemical (allergen) may reach the covered parts either by going through the clothes or by being transferred to the body by scratching. Therefore, it is important to strip

the patient having a suspected case of allergic dermatitis and to determine the extent of the involvement. It is true that for sensitization it may be necessary for the chemical to be rubbed into the thin areas of the skin, either by the friction of the work clothes at points such as the wrist or waist line, or by the friction entailed by the occupational process, or else the perspiration caused by physical labor may so macerate the skin as to render sensitization easy. Nevertheless, after the person is once sensitized, then dermatitis will develop on any portion of the skin where some of the sensitizing chemical is present.

3. Appearance of the Lesions. An acute allergic occupational dermatitis usually begins as an erythema followed by papules and vesicles and when the vesicles break there is oozing and crusting, no matter what irritant is the cause. It does not differ in appearance from dermatitis caused by primary irritants or by sensitization to substances met outside of industry or by sensitization to mycotic infections.

Chronic allergic occupational dermatoses are usually more or less generalized and resemble the chronic lesions caused by substances met with outside of industry. There may be fissuring, lichenification and other characteristics of a chronic dermatitis. Secondary infections with pus-forming organisms or with fungi may considerably alter the picture.

4. Patch Tests. The patch test is of great importance in the diagnosis of an allergic occupational dermatitis. However, it should be used with caution and only those substances with which the patient has already had contact should be applied in the test. Indiscriminate patch testing with sensitizers may not only sensitize the worker to some substance to which he would not have become occupationally exposed, but may also obscure the diagnosis by producing misleading reactions upon subsequent patch tests. Because of this I cannot advocate pre-employment patch testing with sensitizers.

The patch test should be positive in all acute and chronic cases when the proper causative agent is applied to any portion of the skin, except portions thickly covered with epithelium, such as the palms and the soles.

TECHNIC OF THE DIAGNOSTIC PATCH TEST. Before describing the methods used for patch testing I must again call attention to the difference between the primary skin irritants and the sensitizers.

It is obvious that patch testing with strong concentrations of known primary irritants will result in reactions on any skin. This does not mean that patch tests should not be performed with dilute solutions of chemicals which in strong concentration are primary irritants. There are published lists of concentrations of chemicals which dermatologists have used to determine hypersensitivity; these listed concentrations, together with the time they are to remain on the skin, are recommended in an attempt to avoid the primary irritant action of the chemical.[1]

The diagnostic patch test consists in applying a small portion of the suspected substance to a site of normal skin of the patient. This is covered with innocuous impermeable material which is then sealed to the skin by adhesive plaster and left in situ for from one to three days.

The diagnostic patch test may be performed in the following manner:

With liquids: Saturate a piece of 4-ply gauze $\frac{1}{4}$-inch square and apply it to uninflamed skin on the arm or back. The liquid from the gauze should not be permitted to trickle from the patch site. For insulation a 1-inch square of non-waterproof cellophane is used. (Waterproof cellophane consists of regenerated cellulose coated with a water-insoluble resin.) This is sealed to the skin with adhesive plaster about 2 inches square. When smaller pieces of adhesive plaster are used patches are often lost or there is insufficient contact between the test substance and the skin. The reactions which may result from the adhesive plaster are separated from those resulting from the test substance by the uninflamed skin which is in contact only with the cellophane. In performing a number of patch tests, care should be taken to avoid overlapping of adhesive plaster as this will cause intensification of the adhesive plaster reaction.

With powders: In performing patch tests with powders, the powder is placed on a piece of gauze in order to keep the reaction localized. If the gauze is moistened it holds the powder better than when dry.

With solids: When solids insoluble in water are used, it has been found best to dissolve them in a solvent, making a saturated solution, and wetting a piece of gauze with this solution. The gauze is then allowed to dry before being placed on the skin in order to eliminate the action of the solvent. This procedure deposits the precipitated, finely divided substance on the gauze, and brings about better contact with the skin.

When the insoluble solid is of a resinous character, the solution may be painted directly on the skin, the solvent allowed to evaporate, and the cellophane and adhesive plaster applied. If the resin adheres firmly to the skin, it is not necessary to cover it with the cellophane and adhesive.

With ointments: The technic of testing with ointments is the same as with liquids.

While solvents are primary skin irritants they sometimes also act as sensitizers. When it is desired to determine whether a solvent is causing dermatitis by its action as a sensitizer, patch tests may be performed as follows: Mix equal parts of the solvent and a bland oil such as liquid petrolatum or corn oil, in order to buffer the fat-solvent action of the solvent, and patch as for liquids.

When patch testing with unknown chemicals or untried dilutions of known chemicals it is advisable to apply patches on control subjects.

It is usually sufficient to leave the patch on for twenty-four hours but sometimes when patching with low concentrations or with weak sensitizers it may be necessary to leave the patch on for three or four days, but not for more than five days as the patient may by that time become sensitized to the patch itself. This is especially true of fabrics, which contain no strong irritants and to which most people do not react. The reactions should be read not only upon the removal of the patches but every day for at least five days thereafter. This is of special importance in testing fabrics. A late reaction indicates a lesser degree of sensitivity than an early reaction.

MODIFICATIONS OF THE PATCH TEST. Rokstad has suggested a modification of the patch test for testing the primary irritant effect of volatile substances. A celluloid chamber is fixed to the skin with adhesive tape or, in the case of sensitivity to adhesive, with a paste made of 15 gm. zinc oxide, 15 gm. gelatin, 25 gm. glycerin, and 45 ml. distilled water. The irritant solvent to be tested is placed on the skin and covered with the chamber. When applied correctly the chamber should be air-tight and a papule formed by the underlying skin protruding into the chamber. The edematous papule which is thus formed facilitates absorption of the test substance.

Grolnick advocated the use of non-moistureproof cellophane held in place by collodion in order to avoid a possible adhesive tape reaction.

The so-called window patch test was suggested by Guild in 1939, so that constant observation could be made and a controlled alkalinity or acidity could be maintained. A microscopic slide is cut into one-inch squares, the edges are made smooth, and the glass square is fixed to the skin by adhesive on three sides. The substance to be tested is introduced at the open end and then it too can be closed off.

Wedroff has suggested that primary irritants containing volatile solvents as diluents should be painted directly on the skin, or various concentrations in alcohol can be placed dropwise on the skin and left uncovered.

Sulzberger, as well as others, has advocated Scotch cellulose tape as a covering to increase the visibility.

It is often advisable to use a so-called artificial perspiration to moisten the test substance because the *p*H of the perspiration, especially in such areas as the axilla, may play a role in the solubility of the irritant under investigation. The *p*H of axillary sweat is usually on the alkaline side and that on the body proper is on the acid side; *p*H can vary from 5 to about 8. To approximate the *p*H of the perspiration, acidify the liquid used for moistening with dilute acetic acid or alkalinize with dilute ammonia.

INTERPRETATION AND READING OF PATCH TESTS. It requires considerable experience to interpret correctly reactions to patch tests and it is of practical importance to have a common basis for grading reactions. If the relative sensitivity of a worker to the chemical causing the dermatitis could be clearly indicated by the report of the first patch test reaction. it could be determined by repeated patch tests whether he is becoming more or less sensitive in cases in which there is continued contact with the sensitizing chemical. I am convinced that "hardening" or hyposensitization takes place in most workers exposed continually to the offending chemical.

Since the patch test was first employed, gradations of the reaction have been recorded by the symbols 1+, 2+, 3+ and 4+. By this method an erythema on the area of skin to which the chemical was applied is indicated by 1+; erythema and edema by 2+; an erythema, edema, papules and a few vesicles by 3+; and erythema, edema, many vesicles, and in some cases ulceration, are recorded as a 4+ reaction.

Such a method of recording a positive patch test may be useful in indicating the degree of sensitivity to the specific concentration and amount of the chemical used. Additional information can be obtained if patches with differing concentrations are applied. The degree of reaction will be greatest at the site of greatest concentration. It is for this reason that weak concentrations of sensitizers must be left on longer and observed for at least five days after the patches are removed. A reaction not present when the patch is removed but which becomes manifest less than five days after the patch is applied is considered a "delayed" reaction. The delayed reaction indicates either that a low degree of specificity is present or that a weak concentration of the sensitizer was used.

The true allergic reaction as a rule increases rather than decreases in intensity for twenty-four to forty-eight hours after the patch test is removed. Reactions of primary irritation with few exceptions tend to subside after the removal of the irritant.

To report a patch test reaction properly there should be given (1) concentration of the chemical tested; (2) amount of the chemical used; (3) area of skin contacted; (4) site of application; (5) number of days patch test was left on; (6) intervals after removal of the patch at which readings were made. With this information a comprehensive appraisal of the reaction in terms of the degree of sensitivity can be made.

The evaluation of a weakly positive reaction (1+) depends a great deal on the experience of the operator making the patch test. In dealing with a fabric or other substance containing a weak concentration of a sensitizer, a 1+ or 2+ reaction is very significant. This is especially true in industry where dermatitis may not only be due to contact with the sensitizer in low concentration but to the added factor of friction, which is not present in the patch test, with exposure to large amounts of the chemical.

A positive reaction which cannot be reproduced later by the same technic indicates only that at the time the patch test was performed the patient was sensitive to the concentration and quantity of the chemical applied. A 1+ reaction which does not persist for twenty-four hours is probably a false positive or is caused by a mild primary irritant.

A *negative patch test* does not necessarily rule out the test substance as a causative agent. The negative result may be due to one of three causes: (1) under the condition of the patch test the actual mechanism which produces the dermatitis is lacking, i.e., patch test does not equal working conditions; (2) the patient is no longer sensitive; (3) the actual sensitizer was not applied, that is, the case was not sufficiently investigated.

Patch tests may also be negative on a sensitive skin because an insufficient amount of the chemical is contained in the patch. The amount of the chemical to be applied to a given area of the skin when performing patch tests is not yet established. It has been shown that larger amounts of the chemical on the patch will elicit stronger reactions. Patch tests may be negative in sensitive individuals because the allergen is a solid which is not soluble in the secretions of the skin. Water-insoluble solids should be applied to the skin dissolved in a volatile solvent which must be permitted to evaporate before the patch is covered (p. 267). Patch tests may be negative in allergic occupational dermatitis during the period of incubation; after the acute inflammation has passed its peak and is on its way to recovery; after the patient has recovered; or because the amount of the allergen applied in the patch test is not so great as it is in actual industrial exposure, or the skin is not exposed for so long a time; or because the patch test does not force the allergen through the horny epithelium as does industrial exposure; or because the composition of the perspiration at the time the patch test is performed may differ from that during work and thus influence the solubility of the allergen.

When the patch test is positive in allergic dermatitis, it may be accompanied by flare-ups of quiescent sites of the eruption and by systemic symptoms such as malaise and elevation of temperature. Conversely, fresh attacks of dermatitis resulting from allergy to the same causative agent may relight old negative patch test sites to which the causative agent had previously been applied. In non-allergic dermatitis the patch test may be positive only on the sites of the eruption or very close to it, where the skin structure is similar to that of the affected area, and there are no constitutional symptoms present after a positive patch test and no flare-ups of previous sites of eruption.

Management. We have noted that in most instances an allergic dermatitis develops in new workers about one week after they begin work. In many industries in which the worker comes in contact with sensitizers it is an accepted fact that the new worker may develop a dermatitis. In most cases, however, if such a worker is able to keep on working, the dermatitis clears up after a period of time. The workers call it "becoming hardened." In other words, exposure first causes a sensitization, then further exposure causes a dermatitis, and still further exposure may create an immunity. Therefore, new workers who develop dermatitis should not be taken off the job but should be supplied with protective clothing and mild medicaments (see Chapter 17) and allowed to continue at their work in order to give them time to develop an immunity. An immunity so developed lasts for a reasonable time after contact with the irritant has ceased; for instance, it lasts over the week-end, or it lasts after the factory has shut down for a week; but if the worker stays away from work for a month or more, it diminishes so that if he resumes work after a long lay-off, he again must go through the "hardening" process.

Workers who develop such a severe dermatitis that they must stop work in order to recover do not develop immunity as frequently as those who get well on the job and it is often necessary to transfer them to other occupations. There are instances in industry where a worker worked for many years at a certain occupation before he developed an allergic dermatitis. In such cases we have not known immunity to develop upon further exposure.

Such skilled workers to whom a change of occupation means a large financial loss should be given a chance to become immunized by desensitizing injections before they are made to change their occupations. Attempts to desensitize by injecting minute increasing doses of the sensitizing agent have met with success in only a few isolated recorded cases. In view of the work of Landsteiner, Haxthausen, Sulzberger and others, it is suggested that there is a possibility of obtaining better results by injecting minute increasing doses of the sensitizer mixed with a protein such as egg albumen, with fungus extracts, or with the serum of the patient. Non-specific desensitization may be tried, but it has not met with much success.

Workers Susceptible to Dermatitis. Considered from the standpoint of occupation rather than from that of causative agents, occupational allergic dermatitis is often seen among chemists and laboratory workers. It is a well known fact among chemists that many of the organic nitro compounds are sensitizers. I have seen many cases of extreme sensitivity among chemists to such chemicals as dinitrochlor benzol, nitrosodimethyl aniline, and other dye intermediates. So sensitive were some of these persons that they began to itch if a closed bottle containing the chemical was in the room. Photographers who handle developers. many of which are sensitizers; field workers coming in contact with plants; florists; fruit and vegetable handlers; cannery workers; insecticide makers; workers sewing fabrics treated with anti-mildews or other irritant chemicals; rubber compounders; munition workers; and dye manufacturers coming in contact with dye intermediates, constitute the great majority of those with allergic dermatitis by the nature of their occupational contacts.

Non-Occupational Allergic Contact Dermatitis

An allergic dermatitis from contacts known to be other than those arising in occupations may be caused by almost anything. To find the actual cause of a particular case often taxes the ingenuity of the doctor, involves considerable questioning of the patient and a long series of tests. There is no doubt in my mind that careful search will often result in finding a contact allergen which will change a diagnosis of neurodermatitis or atopic eczema or dermatophytid into one of contact or allergic extrinsic dermatitis. The most common causes of non-occupational contact dermatitis are (1) wearing apparel, including jewelry; (2) cosmetics; (3) paints, varnishes and upholstery on articles of furniture; and (4) plants.

(1) **Dermatitis from Wearing Apparel.** *Fabrics.* The majority of such dermatitis is caused by processed fabrics. Unprocessed silk, cotton and wool rarely cause allergic dermatitis. Fabrics worn by the public consist of the basic fabric and all such chemicals as dyes and finishes with which they have been processed to make them suitable for wearing.

UNPROCESSED FABRICS. Sensitivity to silk has been reported but most of the reported cases have been from processed silk. Very few authors differentiate between sensitivity to the raw silk and to the chemical with which it was treated. The eruption described by most of the writers is of the urticarial type. Urbach[2] described an actual case of contact dermatitis from unprocessed silk.

Fabrics made from wool, camel's hair and other animal hairs have been reported as causes of allergic contact dermatitis. There are no reported cases of dermatitis from unprocessed fabrics made from vegetable fibers such as cotton and linen, although dermatitis has been reported as occurring among pickers of flax and also from cottonseed oil (oil of gossypii).

A review of the literature on sensitivity to so-called basic fabrics shows that in most instances the sensitivity tests from which the diagnoses were made were performed not with the actual raw materials but with undyed or unfinished fabrics, so-called "gray goods," which are already partially processed. Perhaps another fallacy in some of the reported tests has been failure to distinguish between the physical irritation caused by "woolly" or rough fabric and an actual allergic reaction. As a corollary, a dermatitis may be caused by the friction of a rough material while a patch test for the purpose of demonstrating sensitivity would be negative.

SYNTHETIC FIBERS. Fabrics for wear are made of processed cellulose (rayon), of a number of synthetic resins, glass and casein.

Cellulose. From cellulose are manufactured the various rayons such as viscose rayon and acetate rayon. While many cases of dermatitis have been reported among the wearers of these rayons, all the cases were from the finished product and not from the unprocessed material.

Synthetic Resins. The best known of the purely synthetic resin fabrics are polymers made from hexamethylenediamine and adipic acid and sold under the trade name of nylon. Although some cases of dermatitis from nylon have been reported, it has been shown that these cases were all caused by a certain finish and not by the nylon itself. Fabrics are now being made on a small scale from vinyl and styrene resins as well as from fiber made from casein. No cases of dermatitis have been reported from them.

Glass. Glass is now being spun into fiber. In order to make these fibers suitable for weaving into fabric, certain resins are used on them. Cases of dermatitis have been reported from such glass fabrics. These cases are due to the resins or the mechanical irritation of the rather sharp fibers and not to allergy to the glass.

Glass wool is made for insulating purposes. Dermatitis occurs in its manufacture and in its use, caused by the mechanical irritation of tiny sharp glass slugs and occasionally from sensitivity to the resin binder (phenol-formaldehyde) which it contains.

SYNTHETIC FILMS. Some of the plastics in sheet form are used for protective clothing. Some of them are also laminated onto cotton or other natural fabrics in order to make them impervious. Rubber hydrochloride, vinyl resins, acrylic acid resins and cellulose acetate are used for these purposes. Dermatitis has been reported from the vinyl, the acrylic acid and the rubber hydrochloride films, but in all these cases it was due either to plasticizers or stabilizers used in the films.

The following plasticizers, stabilizers and modifiers have been causes of dermatitis: tricresylphosphate, triphenylphosphate, dibutyl sebacate, dibutyl tin laurate, dibutyl tin laurate maleate, phenylsalicylate, and resorcin-formaldehyde combination.

RUBBER. Dermatitis from wearing apparel made of rubber has been reported. Gloves, girdles, dress shields, gas masks, condoms and so on have all been reported to cause dermatitis. In all of these cases it was the compound placed in the rubber, such as the accelerator or antioxidants, or compounds formed on the surface of the rubber by "vapor cure" (sulfur monochloride) which have been the actual irritants, not the rubber itself. The following accelerators, antioxidants and so on have been the cause of dermatitis: hexamethylenetetramine, the guanidines, mercapto benzothiazole, tetramethyl thiuram monosulfide and disulfide, paratoluidine, orthotoluidine, triethyl trimethyl triamine.

and the antioxidants phenyl beta-naphthylamine and monobenzyl ether of hydroquinone (the last has caused leukoderma).

The accelerators named are contained in many rubber articles which do not cause dermatitis. They cause dermatitis only when they are contained in the rubber in such quantities that they "bloom" out or if they are so loosely incorporated that they can be leached out by the perspiration. The same statement applies to the antioxidants except monobenzyl ether of hydroquinone. This chemical can cause leukoderma even when it is properly incorporated into the rubber.

Dermatitis from "vapor cured" rubber is caused by the fact that continuous changes take place on the surface of the rubber, resulting in the formation of sensitizing chemicals. Those who develop dermatitis from wearing vapor cured gloves (i.e., surgeons) may prevent dermatitis in the following manner: soaking the gloves in a 5 per cent solution of sodium carbonate for fifteen minutes and then rinsing in water; sterilizing by dry heat and wearing them dry and powdering well on the inside of the gloves every time they are to be worn. The same procedure should be adopted by those sensitive to rubber gloves made directly from latex, because in such gloves the accelerators and antioxidants are more easily leached out by the perspiration.

SYNTHETIC RUBBER. There are several types of synthetic rubber. The first one made in America was neoprene, which is made from acetylene. There are now being manufactured buna S made from butadiene and styrene, buna N made from butadiene and acrilonitrile, and butyl rubber made from butylene and isoprene. Although these synthetic rubbers have been on the market for a comparatively short time and only a little wearing apparel, mostly gloves, has been made from them, some cases of dermatitis have been reported.

These synthetic rubbers are processed similarly to natural rubber and contain accelerators, antioxidants and other compounds. They are cured by heat as well as by sulfur monochloride. Most of the cases of dermatitis from synthetic rubbers are probably caused by the same compounds that cause dermatitis from natural rubber, although synthetic rubber does contain sensitizing substances not present in the natural rubbers.

DYES AND MORDANTS. Dermatitis due to fabric dyes is relatively infrequent among the wearers of the fabrics although for some time it was the common impression among physicians that dermatitis due to wearing apparel was caused by the dyes in the fabrics. When dermatitis is caused by the dyes, it is usually due to an idiosyncrasy to the dye itself or to a faulty process of dyeing, so that there is retained in the fabric some chemical which should not have been present. On occasion, dyes will cause dermatitis if one of the known sensitizing dyes is used.

When dyes themselves have been found to be the cause of the dermatitis it has been usually found that they easily come out of the fabric or "bleed." Conditions on the skin surface may help to determine the "bleeding" of the dyes from the fabric. For instance, some will bleed out in acid perspiration and others in alkaline. Since some of the dyes are soluble in fat solvents, a high fat content on the skin surface may help dissolve them out. It is also to be borne in mind that the dye intermediates are more likely to cause dermatitis than the finished dyes themselves and that under certain conditions, such as the heat of ironing, some dyes will break down into their intermediates.

Faulty dyeing process may cause dermatitis by leaving in the fabric some chemical irritant which should have been removed. For instance in vat dyeing or in mordant dyeing the excess of the oxidizing or mordanting bichromate should be removed before the dyeing is finished; otherwise dermatitis may occur in those handling or wearing the fabric. Wool is often dyed by the aid of a mordant and mordants are also used in certain other dyeing processes. Of the mordants it is the dichromates which have caused dermatitis.

The following dyes have been reported as causing dermatitis: amino-azo-benzene; auramine; brilliant indigo 4G; crystal violet; chrysoidine; hydron blue; iso-rosinduline; indanthrene violet R. R.; ionamine A; metanil yellow; methyl violet; malachite green; orange R; orange Y; ponsol dark blue B.R.; sulfanthrene pink F.F.; safranine; victoria blue; victoria green; and resorcinol component dyes.

Special dyes are used for dyeing of rayon because the ordinary dyes do not easily penetrate the comparatively solid rayon fabric. Dermatitis has not been reported from these special acetate dyes.

FABRIC FINISHES. It has been shown that in most instances dermatitis among the wearers of fabrics is caused by the finishes rather than by the dyes.

Finishes are placed in fabrics to give them a more attractive appearance, such as a luster, better feel and wearing properties, to prevent runs and unraveling, to make fabrics noncreasing and sometimes to hold the crease, and to make them waterproof, mothproof, flameproof, moldproof and insectproof. Some of the finishes stay more or less permanently in the fabric. Other finishes are easily removed by laundering and only a small part may remain after many washings. For this reason finishes which are removed by laundering are reapplied after each laundering.

Starches and sulfonated castor oil were the first finishes used and were applied to enhance the appearance and the feel of the fabric and thus increase its selling appeal. Dermatitis has never been reported from starch, but the author has shown that an improperly neutralized sulfonated castor oil (alkaline in reaction) was the cause of a dermatitis from socks.[3]

Antiwrinkle and Crease-holding Finishes. More recently certain resins have been applied as finishes to make the fabric resistant to wrinkling or to hold its crease and, in the case of stockings, to prevent runs. These resins are usually applied in the dye bath and consist of modified natural or totally synthetic resins.

The author and his associates showed that an outbreak of dermatitis thought at first to be due to a synthetic fabric was really due to a finish containing an ester gum.[4] This finish was used on other fabrics and also caused dermatitis. The new synthetic resin finishes have caused a number of such cases of dermatitis. The resins are applied from solutions or emulsions which leave a thin film of the resin on the fabric after evaporation of the solvents. The resins, ester gums, the formaldehyde type of resin, methyl methacrylate, vinyl, styrene and glyptal resins may be applied in this manner.

Some of the resins when applied in the form of emulsions containing uncured or partially cured resins are completely cured in the heat of the finishing bath and in the heat of the boarding process. Completely cured resins do not as a rule cause dermatitis. When complete polymerization and stabilization do not occur, there may be enough free monomers or uncured resins remaining on the fabric to cause dermatitis in sensitive cases. Actual sensitization by the fabric can of course occur also.

Glycerin-phthalic anhydride resins are used in emulsions containing alkali such as ammonia or sodium hydroxide or triethanolamine. These resins may also contain impurities which are skin irritants. The dicyandiamide-formaldehyde resins may undergo decomposition to form methylamines which may cause dermatitis.

Other resins which cause sensitization dermatitis may be introduced into use as fabric finishes in the future.

Waterproof Finishes. In some of the older methods of waterproofing (1) the fabric was placed in the soap bath followed by alum or other aluminum salts in watery solution in order to deposit aluminum soap on the fabric, or (2) an application of aluminum or lead soap from an organic solvent such as benzene was made. There are no recorded cases of dermatitis from the finished materials proved to be due to waterproofing agents containing these insoluble metallic soaps.

In still another method of waterproofing, the fabric after dyeing and drying is then passed through a solution of paraffin dissolved in a petroleum solvent and again dried over hot cylinders. When japan wax was used instead of paraffin, dermatitis was seen from such coated fabrics because japan and china wax are derived from a tree of the poison ivy family (Rhus vernicifera).

Fabrics have been treated with tar or resins and rubberized in order to make them waterproof. Dermatitis has been seen from such materials only among the processors of the fabrics.

Flameproofing. Canvas and leather gloves, sleeves and aprons are used as a protection by welders to protect them against sparks. These materials may be treated with flameproofing chemicals. Asbestos also is used but wearers of asbestos do not have dermatitis from it, as it is not worn next to the skin.

Cotton and silk are often flameproofed by treating with chlorinated naphthalenes, ammonium sulfamate, boric acid and borate, diammonium phosphate, antimony chloride or other substances. Although workers making clothes from these materials sometimes develop dermatitis and workers processing fabrics with chlorinated naphthalene may develop chloracne, cases of dermatitis among the users of these fabrics have not been reported.

Delustering Agents. Zinc sulfate, barium sulfate, aluminum sulfate and titanium oxides are some of the chemicals used as delustering agents. No dermatitis has been reported from their use.

Mothproofing and Lousicides. Silico fluorides are most frequently used for mothproofing, although the chlornaphthalenes (naphtha balls), chlorbenzene, chlorphenols, synthetic camphor and others are used. The solutions of silico fluorides are usually sprayed on the fabrics. The chlornaphthalene and camphor used in the form of flakes or balls are placed in the clothes or closets. Dermatitis has not been reported from fabrics exposed to these substances.

During World War II and since, it has been found desirable for sanitary reasons and as a protective measure against typhus to treat clothing of our armed forces with chemicals known to kill lice and other related insects. The most widely used and effective agent at present is DDT (dichlor-diphenyl-trichlorethane). It can be used alone or in combination with other insecticides. Other insecticides such as pyrethrum, rotenone (the active principle of derris and cube) and synthetic insecticides may be used.

The synthetic insecticides are usually primary irritants in strong concentrations, and the natural insecticides are sensitizers.

Antimildews. During the war it was found necessary to mildewproof many articles of clothing and equipment made of fabric and leather to prevent their deterioration in tropical climates. Tenting, hammocks, camouflage and mosquito netting, knapsacks, canvas covers of all kinds, interlinings of shoes and many other articles have been treated with mildewproofing agents. They are so precipitated on the fabrics that they will be retained after many washings.

While many chemicals are excellent fungicides, they cannot be incorporated into articles of clothing or equipment which are to be in close contact with the skin because they are primary skin irritants and sensitizers in the concentrations in which they satisfy antimildew performance specifications against molds. Even if such irritant chemicals are incorporated into materials which are not to be used in contact with the skin, such as sandbags and tenting, they have been causes of dermatitis to the workers making those materials. This does not imply that such chemicals should not be used in fabrics which will not be worn next to the skin.

We have tested many of the compounds which have been suggested by our armed forces as mildewproofing agents by means of the "prophetic patch test." Actual field trials have supported the value of this procedure, when properly carried out, to rule out the use of those chemicals which would cause dermatitis.

When some of the antimildews that were irritants were used on fabrics which were also waterproofed by superimposing a wax, the patch tests were negative because the antimildew did not come in contact with the skin. However, under some conditions of manufacture the workers would have sufficient contact to cause dermatitis when the superimposed waterproofing material was rubbed off after continual friction with the workers' skin, thus exposing them to the action of the antimildew.

PREVENTION OF DERMATITIS FROM FABRICS. The fact that some individual may become sensitized to some chemical which is innocuous to others cannot be helped, but chemicals which are known to be powerful sensitizers have been used on fabrics. Manufacturers and processers of fabrics should avoid the use of such chemicals. When they contemplate using chemicals which have not been used before on fabrics they should endeavor to find out the possible irritating properties of the chemically treated fabric. This can be done by means of prophetic patch tests.

PROPHETIC PATCH TEST. Pieces of fabric at least 1 inch square are placed in the form of patch tests on the arms or backs of 200 persons and permitted to remain there from two to five days. A piece of surgical gauze of 4-ply thickness and of similar size is placed on a similar portion of the skin in the form of a patch test to serve as a control. The reactions should be read and recorded when the patches are removed and the sites examined daily for three days thereafter for the appearance of delayed reactions. Ten days after the last reading the procedure should be repeated.

The first series of tests gives reactions only with a primary irritant, or on those who have been sensitized by previous contact with the chemical. The second series will show reactions on those who were sensitized by the first series. Experience has shown that even *one positive reaction in the second series* indicates that the test substance is a strong sensitizer and will cause outbreaks of dermatitis if used by a large group of people. If no sensitization reactions occur in the second series the fabric should be distributed for wear in a small community of 5000 to 10,000 people for several months, and if no cases of dermatitis develop it can be placed on general sale with a fair assurance that it will not cause an undue amount of dermatitis.

Leather. Dermatitis among leather workers is not infrequent because of the many primary irritants and sensitizers used in processing the hides to convert them into leather. However, the incidence of dermatitis due to wearing and handling leather goods is small compared to the millions of users. Dermatitis has been reported from hatbands, gloves, wrist-watch straps, pocketbooks and other leather articles.

Often the chemicals used in processing hides to convert them into leather may be the cause of the dermatitis, but the tanning agents and the dyes have been found to be the most frequent causes of dermatitis among the wearers and handlers of the finished leather goods. Recently another source of dermatitis among those exposed to the finished leathers has been introduced by the addition of mildewproofing agents to the leather. We have encountered a number of instances of dermatitis due to these chemicals, but as yet leather containing the mildewproofing agents has not been used for a sufficient time by the general public for reports of such cases to have appeared.

The majority of the cases of dermatitis due to contact with leather have been of the allergic type. The sensitizing chemicals may have been dissolved out of the leather by water or perspiration. The sensitivity may have been acquired by contact with the chemicals in the leather, or it may have resulted from previous contact with similar chemicals used in other articles of wearing apparel. The following substances remaining in the leather may be the causes of dermatitis:

Dyes. Bismarck brown; amido-azo-benzene; amido-azo-toluene hydrochloride; and chrysoidine.

Tanning agents. Chromates; oak; sumac; quercitron.

Finishes. Fish oil; castor oil; resins.

ANTIMILDEWS AND FUNGICIDES. We have found leather in which the following chemicals capable of producing dermatitis were used as antimildews: mercapto benzothiazole, tetrabrom ortho-cresol, paranitrophenol, pentachlorphenol, salicylanilide and dihydroxy-dichlor-diphenyl-methane.

Lollar[5] performed patch tests with seven antimildews contained in leather in concentrations of 0.75 per cent and less and obtained reactions from parachlorometacresol, phenyl mercuric acetate, ethyl mercuric phosphate, and puratized N-5-X (organic mercurial).

Artificial Leather. Materials designated as artificial leather may be made from cotton fabrics covered by cellulose nitrate and vegetable oils, synthetic resins or rubber solution, or latex may be impregnated into cotton or loosely felted papers or napped soft felted fabrics. In some instances the cotton fabrics are covered with plastics. Sheets of artificial leather may be made from loose fibers and scrap leather which are compressed after mixing with linseed oil. The grains of the different leathers are then put on the surface by embossing machines or engraved press plates. Concentrated uncoagulated pastes of compounded latex and fibers are dried, pressed and vulcanized in another process of making artificial leather.

Dermatitis may occur from such artificial leather from the dyes, the resins, the formaldehyde, sulfur, the antioxidants and other chemicals used in its manufacture.

SHOES. Dermatitis from shoes has been frequently reported in the literature. A number of instances of dermatitis from shoe polish have also been observed. Such instances have been more frequently reported in the European literature, probably because Americans are not in the habit of polishing their own shoes as are Europeans.

It is hard to conceive of a dermatitis from the outer leather of the shoes, since there is very little contact with the skin of the foot. The chemicals incorporated in the outer leather would have to go through the backing and through the socks in order to produce a dermatitis.

The inner lining of the shoes as well as the backing contains chemicals which may cause dermatitis. The backing of the shoes contains adhesives, antimildews and fungicides. In a number of instances artificial leather may be used on the inside of the shoes.

Furs. There are many reported instances of dermatitis due to the handling and wearing of furs. While a dermatitis among the wearers of furs may occur from the mechanical friction of the coarse hairs against the skin or from a sensitivity to the unprocessed fur, such occurrences are rare. In the majority of such cases it is due to the dyes and the tanning agents.

Since the non-hairy hide of the pelt is covered by lining, only the fur itself comes in contact with the skin. Thus the chemicals used for tanning and dressing the fur rarely cause dermatitis, especially since they are present in only traces in the hair of the fur. It is the dyes and the mordants used with them which are applied to the hairs that cause the dermatitis from wearing of furs. It is necessary for the wearer to be sensitized to these chemicals before the garment is worn or to have been sensitized by wearing the garment in order to develop dermatitis. Furthermore, in order to cause a sensitivity the furs must be so poorly dyed that they are leached out by perspiration or moisture. It is possible that, once sensitivity has developed, even a well dyed fur may cause dermatitis.

Paraphenylenediamine has been the chief cause of dermatitis from fur. The other oxidizing dyes, aniline black and ortho amino phenol, may also cause it. The chrome mordants are also possible etiologic factors.

Paraphenylenediamine is a white crystalline substance which itself is comparatively non-irritant. For use on a fur it must be oxidized. The first oxidation product is said to be quinone diamine, which is an unstable compound capable of producing local irritation of the mucous membranes. This chemical is said to be the actual cause of dermatitis from paraphenylenediamine. Further oxidation results in the formation of a chemical known as Bandrowski's base, which is not yet the final black oxidation product but is not supposed to be irritant.

PREVENTION OF DERMATITIS FROM FURS. The reduction of the incidence of dermatitis among the users of furs is in the hands of the dyers. In recent years they have been aware of this fact and have processed the furs with greater care so that now we rarely see reports of cases. The preventive measures used by the dyers include the use of weak solutions of the dyes frequently applied or applied for longer periods rather than concentrated solutions for short periods, the careful oxidation of the dye and the thorough removal of excess dyes by washing and drumming.

Jewelry. Most instances of dermatitis from jewlery have been from metals, but dermatitis may also occur from ornaments made of incompletely polymerized or condensed plastics. Cases of dermatitis have occurred from rings, earrings, necklaces, lockets, bracelets, wristwatches and straps, spectacle frames and metallic trimmings on hand bags.

Most jewelry and metal ornaments are alloys and the sensitivity is usually to one of the metals in the alloy. This should be borne in mind and when testing for the actual metal to which the patient is sensitive the composition of the alloy should be ascertained. Nickel, cobalt, platinum, chromium and gold have all been reported as causing allergic dermatitis.

Feathers. Contact dermatitis from feathers in wearing apparel is a rarity, since most feathers are used as ornaments on hats or other objects, and there is but little contact with the skin. In the past, contact dermatitis due to feathers has been reported mainly among children who had contact with the feathers in pillows and bedding.

Diagnosis. Dermatitis from wearing apparel is not difficult to diagnose once suspicion has been established. The eruption begins at the place of contact with the offending material, usually five days or more after the garment has been worn. This is the period of incubation necessary for the sensitivity to become established. The eruption may appear sooner if the person is already sensitive to the chemical in the wearing apparel which causes the dermatitis. The eruption is usually confined to the areas of the skin touched by the offending material. In exceptional cases, however, a generalized eruption may be present and sometimes systemic symptoms such as elevation of temperature may accompany the dermatitis.

PATCH TESTING WITH WEARING APPAREL. It is best to use large pieces of the material, because they contain more of the allergen. Pieces should be at least 1 inch square. The patch may remain on for two to five days, and if there is no reaction upon removal of the patch the site should be inspected each day for three days for the development of delayed reactions. If a reaction is obtained, attempt should be made to ascertain whether it is caused by the finish, the dye or the basic fabric.

Furs. In patch testing with fur the test should be carried out with the hairy side of the fur. If it is positive, rub the fur vigorously with a piece of gauze; should the gauze become discolored, the fur is so-called "dirty fur." A patch test should then be carried out with the gauze discolored by the dye. While most cases of fur dermatitis are due to dye, a dermatitis due to fur itself may be found occasionally.

Shoes. In investigating suspected cases of dermatitis due to footwear, it is useless to patch test with the material on the outside of the shoe. Rather, patch tests should be made with the backing. In some instances the leather on the inside of the shoe, such as the tongue, the inner sole and the sock lining, may be the cause of the dermatitis, but rarely if ever the outside leather. The chemical which causes the dermatitis must get through the sock or stocking. Therefore it is worthwhile to patch test with the sock or stocking (before washing), which should contain the reacting agent.

(2) **Dermatitis from Cosmetics.** Although reports of dermatitis from cosmetics are not infrequent, if we consider that cosmetics are universally used the incidence of cosmetic dermatitis is very low.

Occupational dermatitis among the makers of cosmetics does not frequently occur but dermatitis among beauty parlor workers is fairly common. Hair dressers may have dermatitis from soaps, tars, petroleum oils, hair wavers, hair straighteners, etc. Most of these act as primary irritants on workers who unduly expose their hands or who have some anatomic or physiologic defect of the skin. Such cases of dermatitis can be prevented by the use of rubber gloves.

It is dermatitis that occurs among the users of cosmetics which concerns us most here. Outside of dermatitis from the improper use of depilatories, cuticle removers, perspiration inhibitors, bleaching and freckle creams, hair wavers and straighteners which contain primary skin irritants, the majority of skin injuries among the users of cosmetics belong to the allergic class, and have been caused chiefly by synthetic hair and eyelash dyes, lipstick, nail lacquers, and lately there was an outbreak from hair lacquer containing a synthetic resin as a substitute for unobtainable shellac. The accompanying list includes the chief cosmetics reported as having caused dermatitis, both allergic and non-allergic.

While cosmetics as a class rank among the safest of substances in so

COSMETICS REPORTED TO HAVE CAUSED DERMATITIS

Cosmetics	*Chemical Causes*	*Type of Dermatitis*	*Comparative Frequency*
Creams	Petrolatum Triethanolamine Methyl heptine carbonate Phenols Mercurials	Allergic	Rare
Deodorants	Aluminum salts Perfumes	Primary irritant and allergic	Fairly common
Depilatories	Sulfides Alkalis Thallium acetate (systemic poison)	Primary irritant	Fairly common
Hair wavers, straighteners and lacquers	Alkalis Resins Reducing agents Thioglycolates	Primary irritant and allergic	Fairly common
Hair dyes and Eyelash dyes	Oxidation dyes, i.e. Paraphenylenediamine Paramido phenol Orthoamido phenol Paratoluenediamine Metatoluenediamine	Allergic	Now rare but frequent when these dyes were first introduced
Lipstick	Dyes, chiefly the eosin group which are photosensitizers Perfume Methyl heptine carbonate	Allergic	Fairly common
Nail lacquers	Synthetic resins of formaldehyde and ester gum types. Dyes: Eosin, rhodamine B and deep maroon	Allergic	Fairly common
Perfume	Oil of bergamot Methyl heptine carbonate Synthetic jasmine Linalool Eugenol Copper	Allergic	Rare
Powders	Dye Perfume	Allergic	Rare
Soaps Cleaners Synthetic detergents	Alkalis Phenols	Defatting action on skin and sensitizer	Fairly common

far as producing dermatitis is concerned, yet there are occasional outbreaks of dermatitis among the public from new and untried cosmetics. The cosmetic industry owes it to the public and to itself to spare no effort in order to place only safe cosmetics on sale. This can be done by testing the effects of new cosmetic formulas on the skin before placing them on the market. Based on the author's extensive experience in the field the following procedure is suggested.

Prophetic Test. Before placing a new formula on the market, covered patch tests should be performed on at least 200 subjects with the formula, using as a control an old formula which has been on the market for years, and which has caused no unusual number of complaints. The closed patches should remain on for forty-eight hours after which the reactions should be read each day for three days in order to observe late reactions. The number of reactions obtained from the new formula should not exceed the number obtained from the old.

Ten days after the last reading of the reactions, covered patch tests of both new and old formulas should be reapplied on the same 200 subjects and allowed to remain on for forty-eight hours, and the reactions again read each day for three days after removal of the patches. If the number of subjects showing sensitization reactions from the new formula exceeds the number showing sensitization reactions from the old formula, the formula is unsafe. These tests will give an idea of the relative skin-irritating and sensitizing properties of the new formula as compared with the old one, but will not give an accurate idea of what may happen under conditions of actual use. Therefore the following additional tests should be performed.

The same 200 people should actually use the old and the new cosmetic on opposite sides of the body each day for a period of four weeks. If no cases of dermatitis result from the new formula it is safe to place on trial sale. If only one case results then another group of 200 people should be subjected to the actual use test. Only if no cases of dermatitis result among these is it safe to place the cosmetic on trial sale. If more than one case of dermatitis occurs among the first 200 subjects after four weeks of actual use the cosmetic is unsafe.

By trial sale is meant the sale for a period of not less than one month (if no cases of dermatitis are reported before this time) in only one community where between 500 and 10,000 packages of the cosmetic are to be sold. If no cases of dermatitis are reported during the trial sale, then the cosmetic is safe. If cases are reported during the trial sale, the manufacturer should employ a competent dermatologist to investigate them and determine the actual cause. The continued sale of the cosmetic or its withdrawal from the market should depend on such an investigation.

Diagnostic Tests. In trying to ascertain whether a cosmetic is the cause of dermatitis, it is better to apply the cosmetic daily to the same test site of skin for at least four days in the manner in which the cosmetic is actually used, rather than in the form of a patch test. This is because cosmetics when used are not covered and usually a large part of the substance disappears from the skin by evaporation. Covered patch tests do not permit such evaporation, and many cosmetics which are harmless in actual use may give positive patch tests when applied in the form of a covered patch.

In performing patch tests with cosmetics which may contain photosensitizing materials, such as lipstick and dyes, the test should be performed on uncovered portions of the body such as the wrist, the V of the neck or the like, because the photosensitization is only manifest on parts which are exposed to light.

(3) **Dermatitis from Furniture.** New furniture or new paint, or new upholstery on furniture, should not be overlooked as a possible cause of allergic contact dermatitis. A careful history of the eruption and its location may point to such a cause. This can then be verified by patch tests. Do not patch test with thinners; they are primary skin irritants. Patch test only with the dried paints, varnishes, or lacquers which are scraped off the painted furniture. The technic of testing paints and upholstery is identical with that previously described (p. 267).

(4) **Dermatitis from Plants.** Dermatitis from plants is of the allergic type although the active ingredients of plants in pure form are often primary irritants. Plants are a frequent cause of allergic contact dermatitis. They may be encountered in parks, woods, fields, gardens and in the household.

Dermatitis has been reported from several hundred plants, woods, flowers, fruits and bulbs. The members of the family Anacardiacea are probably the most frequent causes of plant dermatitis. Poison ivy, poison oak, poison sumac, Japanese lacquer, cashew nut shell liquid, Indian marking nut, the South American plant litre, are notorious dermatitis-producing members of this family. The active ingredients of these plants are related polyhydric phenols, differing but slightly in chemical structure. They are primary irritants in strong concentrations.

Some of the plants are photosensitizers, as for instance bergamot, buckwheat, fig and certain grasses. In obscure cases of eczema the possibility of contact with household plants should not be overlooked.

For a more complete discussion of dermatitis venenata, with especial reference to ivy poisoning, see the following chapter.

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16. Allergic Dermatitis: Dermatitis Venenata

ROBERT A. COOKE

INCLUDED under this classification are the lesions caused not only by contact with poison ivy (Rhus toxicodendron, Toxicodendron radicans), but also with sumac, primula, geranium, chrysanthemum, tulip, gladiolus and many others. Chemically the allergen in all these plants is of the same order—an alcohol-, ether- or acetone-soluble polyhydric phenol, which is not, save for rare exceptions, of itself primarily an irritant, and is contained in the root, stem, leaf, flower or pollen.

In spite of the chemical relationship, there is clinical evidence of specificity of certain of these allergens. For example, with florists handling both chrysanthemum and tulip, one florist may be allergic only to the chrysanthemum and the other only to tulip, although contacts with both are equally adequate to incite a dermatitis if the sensitization exists. The clinical lesion is practically identical for all allergens of this type, although it is a fact that sumac produces a much more striking edema than any of the others.

The contact resulting in dermatitis is usually a direct one with the plant, but may be indirect from handling clothing that has been exposed, or stroking the dog that has been hunting through the brush. The allergen may also be air-borne, for very severe attacks have resulted from standing in the smoke of burning brush, as the irritant adheres to the carbon particles in a highly active state.

The eruption begins twenty-four to forty-eight hours after exposure, and at first appears at points of contact on the exposed parts of the body. However, it has been shown that the allergen is present in the serum of blebs and blisters, and thus the rash is easily spread by hands or clothing to other covered portions of the skin. The rash reaches its height in five to seven days, and the skin gradually returns to normal after a week or ten days, the time depending upon the severity of the lesion. When exposure is continuous, as in the case of florists, the lesion usually remains as long as exposure lasts.

Diagnosis

The clinical diagnosis of plant dermatitis is usually not difficult, especially that resulting from Rhus, for the attacks usually occur in late spring or summer following an outing in the country. In cases of occupational contact the history is definite. The diagnosis may be

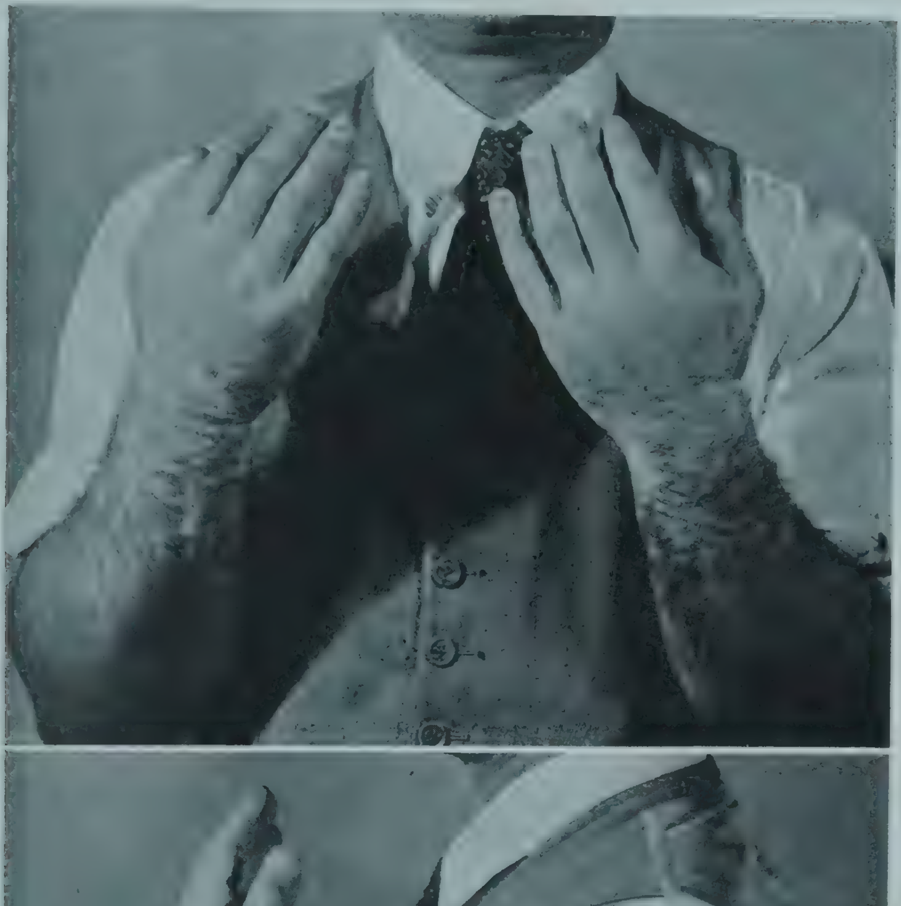

Fig. 26.—Extrinsic allergic dermatitis. Dermatitis venenata.

confirmed by the patch test, as in all types of allergic external contact dermatitis.

Method of Patch Testing. On account of the greater affinity of the active substance for an oil solvent than for the skin, testing with dilutions of ivy in oil is, in general, unsatisfactory. One per cent and 0.1 per cent dilutions of the basic resinous substance in absolute alcohol are used as follows: 0.025 ml. is applied on a blotter under an adhesive patch and left for two days. It may be removed earlier if irritation, indicating the developing dermatitic lesion, should be experienced by the patient. In patients tested for the first time the weaker dilution (0.1 per cent) is used; if the result is negative the 1 per cent dilution is applied. If this is negative, either the solution has deteriorated or the susceptibility of the patient is not sufficient to warrant treatment.

Using the alum-precipitated pyridine ivy "extract," 1:100 and 1:500, of Spain and Strauss (see p. 536), results comparable to those with the alcoholic extracts are obtained.

Treatment

This is preventive and specific. Symptomatic therapy is given in Chapter 17.

Preventive Therapy. Avoidance of contact is, of course, the method of choice for those known to be highly susceptible, and whose occupation or mode of life and environment make it possible.

The use of a protective ointment*, originated by Schwartz et al., is effective and it should be applied prior to any expected contact.

Specific Therapy. For those who are very susceptible and whose environment makes avoidance impossible, benefit is derived from specific therapy for purposes of immunization, using one of the various preparations of the allergen adapted to the particular case, that is, the resin of ivy, tulip, chrysanthemum, etc.

Preparations. Commercial extracts are available, and if used they should be given according to their accompanying directions.

The basis of all preparations is essentially the same, whether it be poison ivy, chrysanthemum, primula or any other required. The active material is derived from leaves, tubers, roots, bark or flowers. Leaves and flowers are easier to handle.

There are several methods of preparing the resins for testing and treatment (see pp. 535–537)—an alcoholic extract, a solution of the ether-extractable substance in oil, and recently an alum-precipitated pyridine "extract" in saline recommended by Strauss and Spain.

Prophylactic Therapy. ORAL. One-tenth per cent poison ivy or other plant phenol in oil (60 ml. is ample for the four months' treatment).

Beginning at least four weeks in advance of the expected season, take doses as follows in milk or fruit juice:

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* West Protective Cream No. 77—West Disinfecting Co., 42–16 West, Long Island City, N. Y. See their pamphlet on "Protective Safe-guards Against Dermatitis."

1st week	2 drops	twice	daily	for	one	week.
2nd “	4 “	“	“	“	“	“
3rd “	6 “	“	“	“	“	“
4th “	8 “	“	“	“	“	“
5th “	10 “	“	“	“	“	“

Then 10 drops daily from the 6th to the 12th week.

SUBCUTANEOUS OR INTRAMUSCULAR. On account of the stability of the active substance in oil such preparations are preferable to those in alcohol. Injections are started at least four weeks in advance of the earliest recorded attack according to the following schedule:

Dose	*Interval*	*Dilution in Oil*	*Amount*
1.		0.01 per cent	0.1 ml.
2.	After 5 days	“ “ “	0.3 “
3.	“ “ “	“ “ “	0.5 “
4.	After 1 week	0.1 “ “	0.1 “
5.	“ “ “	“ “ “	0.3 “
6.	“ “ “	“ “ “	0.5 “
7.	After 2–4 weeks.	1.0 “ “	0.1 “
8.	“ “ “	“ “ “	0.3 “
9.	“ “ “	“ “ “	0.5 “
10.	“ “ “	5.0 “ “	0.2 “
11.	“ “ “	“ “ “	0.3 “
12.	“ “ “	“ “ “	0.3 “

Note: Some patients do not tolerate a dose above the sixth. In such cases the top tolerated dose is repeated every 2 to 4 weeks.

ALUM-PRECIPITATED PYRIDINE IVY “EXTRACT.” The following dosage schedule for injection treatment is given by Spain and Strauss:

Initial dose	0.1 ml. of 1:50 dilution
After 7–10 days	0.4 ml. “ “ “
“ “ “	0.8 ml. “ “ “
“ “ “	0.2 ml. “ 1:5 dilution
“ “ “	0.5 ml. “ “ “

The top dose may be repeated once each two weeks during the summer, and continued upon a perennial basis, once monthly during the winter.

Phylactic Therapy. During an acute attack a few injections of the ivy extract seem to relieve symptoms and shorten the attack.

POISON IVY IN OIL. Intramuscular or subcutaneous injections using the 0.1 per cent solution in doses of 0.1 to 0.2 ml. are given every second day for four to six doses.

ALUM-PRECIPITATED PYRIDINE IVY “EXTRACT.” Subcutaneous injections of 0.1 ml. of the 1:500, or more often the 1:100, dilution are administered every two to four days. Occasionally small increases in the dose are made.

Results. There is no question but that a very practical degree of protection is afforded by the small and gradually increased doses of the active substance of any one of these plant phenols. Chewing of tiny pieces of the first spring shoots of ivy has been a practice of the Indians for centuries, and is in use today in many rural areas. This method has the disadvantage that too large a dose may be taken. This might give rise to stomatitis or incite gastroenteritis, or some other equivalent of a dermatitis.

In some instances there seems to have developed an immunity of considerable permanence, just as there may be after a severe attack of ivy dermatitis. This is not the usual result and cannot be counted on. Most patients, especially those highly susceptible, seem deficient in the ability to maintain protection and require repeated courses of therapy each year.

17. *Allergic Dermatitis: Symptomatic Treatment*

DUDLEY D. STETSON

TREATMENT of the eczematous skin is carried out by internal and external remedies, as well as by such general measures as rest and diet. All of these measures are to be adapted to the actual clinical condition of the skin at the time the patient is seen. The state of the skin governs the choice of measures to be taken and the remedies to be used. This is especially true in the matter of local medication.

General Care

Rest. During the acute attack, rest is most important. The ideal way to secure this is by hospitalization. If this cannot be done, every effort should be made to secure quiet, relaxation and freedom from domestic annoyance and business worries. Rest is just as important in children as in adults.

Diet. For *children and adults* the diet should be nourishing, properly balanced and devised to suit the preferences of the patient as much as possible. Drastic deprivations of favorite, proper foods accomplish nothing unless prescribed from the standpoint of allergy. There is a general belief that "acid foods" are injurious but this is not true. It is well to reduce tea and coffee to avoid the wakeful effect of caffeine. Foods that may produce flushing of the skin, such as mustard, horseradish, pepper and curry, should be used in great moderation as they are liable to increase itching. Very hot drinks will have this same effect and alcohol acts in the same way unless well diluted. Short, strong drinks, such as cocktails, should be avoided.

In *eczematous infants* allergies to important foods as milk and egg are not uncommon. Their importance is derived not so much from the fact that they cause eczema, which they rarely do, as that they may produce an acute gastro-intestinal disturbance and urticaria. The latter is certain to produce an exacerbation of the acute eczema.

Babies who are overweight should be reduced by the elimination of fats, and starches should be restricted. If foods are determined causes of eczema they must be strictly avoided.

Constipation. In all cases of acute dermatitis, attention must be paid to the intestinal tract. Thorough catharsis is indicated at the beginning of treatment, and the bowels should be kept free thereafter by gentle laxatives as indicated. If constipation can be corrected by diet so much the better.

Bathing. There is a widespread belief that no eczematous skin should be bathed. This is not true. It is true, of course, that soap and water washing of the acutely inflamed skin will increase the itching and discomfort, and patients quickly learn this. Even in these acute cases, a lukewarm, plain water tub or shower may occasionally be taken without harm. The drying of the skin must always be done by patting with a soft towel, never by rubbing.

Medicated baths are of little use as a rule. A handful of sodium bicarbonate may be added to a tub of water, if desired, but is not very effective in the control of itching. Starch baths are of occasional use. The starch must be moistened with cold water, and the mass then heated until the starch becomes translucent, when it may be added to the water in the tub. About a pound of starch to the tub of water will do.

The temperature of the bath water is important. It should be as near the body temperature as possible, but should be warm enough to be comfortable to the patient. The patient may be allowed to select the type of bath and the temperature that gives him the most comfort.

Local Applications. *Heat.* While a hot bath will increase skin congestion and itching, a very hot towel applied to a limited area is an effective way to stop itching temporarily. It should be wrung out of very hot water and closely applied to the itching area. When it no longer feels hot, it should be replaced by another. The towels must be very hot and quickly wrung out as dry as possible. Four or five such applications will usually stop the severest itching for a considerable time, and will do no damage to the skin.

Cold. Cold may be applied by means of ice bags or towels wrung out of ice water. Some patients prefer it to heat, but the antipruritic effect is less lasting.

Sedation. While it is not possible to affect the eczematous process directly by internal medication, much can be accomplished by indirect drug action. Sedation is most important. The best drugs for this purpose are the barbiturates and elixir of phenobarbital is one of the best. This may be given in teaspoonful doses, three or four times a day, and in larger doses if necessary. In addition to this, seconal or nembutal, or a similar quick-acting barbiturate, may be given one-half hour before retiring. Bromides may be used but are not so effective as the barbiturates. The fact that barbiturates and bromides may occasionally cause skin eruptions is no contraindication to their use since they are no more liable to cause drug eruptions on the eczematous skin than on a normal skin.

These drugs do not have any direct effect on itching, but indirectly they are very helpful through their general quieting effect. Unfortunately, there is no known drug having antipruritic properties when taken internally. Epinephrine and ephedrine are very useful in relieving the itching of urticaria but are of no use in eczema. In fact, their stimulating properties may be harmful. In some patients itching may be relieved by aspirin in 0.5 to 1.0 gram doses. This is especially valuable at night, with or without a barbiturate.

All of these drugs may be used in children with proper reductions in dosage.

Other Medication. In purulent infections (pyoderma) penicillin or sulfonamide therapy is indicated.

Local Medication. The choice of the local remedies to be used will depend upon the type of eruption to be dealt with, whether it be simply red and dry, moist, oozing, crusted, purulent, or the red thickened skin of the long-standing case. The intensity of the itching also greatly influences the choice of remedy as does the location of the eruption, whether generalized or limited in area and whether located on the hairy or non-hairy skin. Two or more of the above types of eruption may exist at the same time and require different local treatment.

Formulas for the various remedies mentioned here are to be found in the section on Prescriptions, pp. 296–299.

Erythema—Redness. This is a simple redness of the skin which may occur alone or combined with other types of eruption. It is usually accompanied by itching and burning. It may occur in small patches only, or be very extensive. Powders, lotions and very light ointments should be used. Heavy ointments and pastes are liable to increase the itching and the feeling of heat. Powders No. 1 or No. 2 or ordinary bath powder may be used. Any of the clear lotions or powdery lotions given here may be used. Oily lotions are usually not so satisfactory. If for any reason an ointment is desired it should be the rose water ointment of the U.S.P., with or without the addition of 1 per cent phenol to relieve itching. Any of the solutions given here for wet dressings may be used to wet the skin as often as the patient desires, or wet dressings may be applied in the regular manner.

Papular Eruption. This consists essentially of red papules on a reddish base, usually occurring in variously sized patches, but the papules may be diffused more or less evenly over large areas. This papular type is more often found in adults than in children and is usually found in the more chronic cases. The itching is usually intense and requires the stronger antipruritic remedies to control it. Any of the lotions, ointments or pastes given here may be tried. The mild solutions for wet dressings will accomplish little unless required to subdue vesiculation caused by scratching. Pastes frequently do very well, especially paste No. 2. The coal tar preparations are often very helpful and may be used as lotion No. 10 or ointment No. 6. Showers or tubs without soap may be permitted.

Moist, Oozing Vesicular Eruption. This type of eruption is frequently met with and is most distressing to the patient. The first thought here should be wet dressings, done with solutions No. 1, 2 or 3. Solution No. 1 is the best for general use. Solution No. 2 is more astringent, and No. 3 has more antipruritic effect than the others. Ointments and oily lotions should be avoided as they will increase the oozing. Powders and powdery lotions should not be used because they may cake and become very uncomfortable. The caking also interferes with drainage and increases the danger of secondary infection. After the oozing has ceased, a very light ointment such as No. 1 or No. 4 may be cautiously tried. If this causes a return of the weeping, the wet dressing must be resumed.

Poison Ivy Dermatitis. The dermatitis caused by contact with poison ivy is indistinguishable from that caused by the other members of the Rhus genus—poison oak and poison sumac. From the standpoint of local treatment, it is of no help to know which plant caused the trouble.

The local treatment of ivy dermatitis depends upon the state of the eruption when it is seen by the physician. The type of the eruption depends upon its duration, the degree of sensitiveness of the skin, and the intensity of contact between the plant and the skin. The patient should be made to realize that after the eruption has appeared local treatment will give much relief but, since the skin has been actually damaged, time will be required for healing as it would in the case of a burn or other injury.

While blistering is the typical sign of ivy dermatitis, this is preceded by redness, burning and itching. Redness and vesiculation may occur at the same time on different parts of the skin. The majority of ivy eruptions, when seen by the physician, are vesicular. The vesicles usually occur in streaks or patches, forming a pattern which corresponds to the areas touched by the plant. When vesiculation does not occur it indicates that the contact with the plant was not very intense, or that there was indirect contact such as might occur when a towel has been inadvertently thrown down on poison ivy and subsequently used on the skin. Some of the most extensive cases of poisoning have occurred in just this way.

In both types of eruption, vesicular and erythematous, wet dressings will give the surest and quickest relief from the burning and itching. The wet dressings should be applied in the manner described on page 297, using the solutions mentioned on that page. The patient may be allowed a daily tub or shower with moderate use of soap. Scrubbing with the view of breaking the blisters will only increase discomfort and delay healing. If the vesicular eruption has been neglected, crusts and secondary infection may occur. These should be dealt with in the manner suggested on page 295.

After the subsidence of the more acute symptoms as well as between periods of applying the wet dressings, the powdery lotions mentioned on page 298 may be used. There is no reason why ointments should not be used, but patients usually prefer lotions as being easier to apply and cleaner.

The bromides and barbiturates, preferably the latter, may be prescribed for sleeplessness as required.

Purulent Eruptions—Impetiginous Eczema. The purulent type of eruption does not originate as such. It is merely surface infection brought about by bacteria growing in the serum of the weeping eruption. In neglected cases there will be crusts of dried serum and pus. The area underneath the crusts is ideal for the further growth of the pus organisms, hence it is important to remove these crusts. Here again the wet dressings are to be used. They will not only soften and remove the crusts but will also have a favorable influence on the underlying weeping condition.

If the eruption is extensive and especially if the trunk is involved, the tub bath should be employed. The patient may soak in the tub of plain warm water for five minutes or more. If the crusts are very hard, a little soaping with a plain white soap may be allowed. Any possible irritation from the soap will be compensated by the removal of the dried and decomposing serum. After the soaping, the skin must be thoroughly rinsed free of all trace of soap. One such soap bath will usually suffice to remove the crusts. If the pus formation continues, a daily bath in plain water may be given. This is a situation in which the physician must be guided by results.

After the pus formation has ceased, the treatment should be that indicated under the heading of weeping eruption. In the purulent eruptions, a mild, ammoniated mercury ointment, such as No. 5, will often produce a very prompt result. Boric acid ointment U.S.P. is also useful if the ammoniated mercury proves irritating. Sulfonamide ointments should be avoided on account of the danger of sensitization. Oral therapy with penicillin or sulfonamide, or other antibiotics, is indicated.

Dry Thickened Skin. This condition is frequently found in long-standing eczemas. It may be generalized or occur in limited areas only. It may be combined with one or more of the conditions previously mentioned. In typical cases the skin is obviously thickened and has a harsh leathery feeling. It is rather dark red and shows a brownish pigmentation in long-standing cases. The itching is usually severe but may be very slight. If intense in limited areas, the hot towels previously mentioned are very helpful.

Since these cases are of long standing, the patients almost invariably have had much experience with all sorts of local remedies. They frequently settle on some simple oil, such as light mineral or olive, which they apply often enough to keep the skin soft as possible. It is not always wise to change the patient's well-tried routine. Light mineral oil U.S.P. is best for this softening effect. The heavy oil is not nearly so satisfactory. Olive oil and cocoa butter become objectionable after a time on account of the odor. Cottonseed oil and sweet almond oil are satisfactory. The rose water ointment of the U.S.P. is good, but it *must* be made according to the U.S.P. method.

With this type of skin, bathing may well be left to the judgment of the experienced patient. Most of them avoid soap as much as possible. Some find the new soapless detergents, such as Acidolate, to be satisfactory and relatively harmless cleansers.

On this type of skin almost any kind of local remedy may be tried without fear of damage. Powders are useful to reduce friction from the clothing. Powdery lotions usually do no good. Oily lotions are more acceptable, and the alcoholic lotions are useful in controlling pruritus. The coal tar ointment No. 7, the coal tar paste No. 2 and the coal tar lotion No. 5 should be tried, as coal tar is probably the most helpful single drug. In these cases, it should be remembered that all antipruritic remedies are prone to lose their effect after a time. They must be strengthened or changed from time to time. Very strong applications may become irritating if continued too long. Relief from itching, however, is much to be desired since scratching and rubbing definitely aggravate the eruption, which in turn increases the itching. It is characteristic of this condition to have acute exacerbations in which there may be areas of weeping with subsequent crusting and impetiginous infection. It is during these periods that the patient is most apt to seek a physician for relief. During these acute attacks the roentgen ray, properly used, is a most valuable remedy (p. 300).

Prescriptions

Powders. Although little is to be expected from powders in the way of active medicinal effect, they are decidedly helpful at times. They are cooling and help to reduce the friction of the clothing. They are clean and easy to use. They should be liberally applied to dry surfaces only. They may be used on top of a lotion or ointment to mitigate stickiness or oiliness. The purified talc of the U.S.P., powder No. 3, is the simplest of all powders and one of the best. Powders No. 1 and 2 may be used interchangeably with No. 3. Powder No. 4 may have a little more antipruritic effect than the others.

	Powders	*gm. or ml.*
No. 1.	Boric acid	15.0
	Starch	15.0
No. 2.	Boric acid	5.0
	Purified talc	
	Zinc oxide āā to make	30.0
No. 3.	Purified talc, U.S.P.	
No. 4.	Camphor	3.0
	Zinc oxide	
	Starch āā to make	30.0

Wet Dressings. The wet dressing is made preferably with gauze, but any soft porous cloth may be used. It should be thick enough not to dry out too quickly. It should not be covered with anything that will interfere with evaporation, or the cooling effect will be lost. The dressing should be kept continuously wet, not allowed to become alternately wet and dry. It should be in actual contact with the skin at all points, not allowed to bulge away from the skin leaving air spaces. Solution No. 1 may be used under all conditions but is especially useful in the presence of secondary infection. Solution No. 2 is more astringent and will perhaps stop weeping better than No. 1. Solution No. 3 has a greater antipruritic effect than the others through its camphor content.

Solutions for Wet Dressings

No. 1.	Saturated solution of boric acid	
No. 2.	Solution of aluminum acetate, N.F. Dilute with 10 parts of water.	(Burow's solution)
No. 3.	Saturated solution of boric acid Camphor water	Equal parts.

Lotions. Lotions are of three main types—those containing powder those containing oil and clear lotions usually containing alcohol. Those containing oil are more properly known as liniments. Powdery lotions should be applied only to the dry and unbroken skin. If applied to an oozing or excoriated surface they will cake and cause discomfort in addition to being difficult to remove.

Calamine or neo-calamine is frequently added to lotions for the pink effect. It adds nothing to the therapeutic effect, and patients usually prefer a white lotion. Glycerin is added to lotions for its softening effect. It may be increased or decreased as desired in any of the formulas given here. Menthol, phenol, camphor and solution of coal tar are added to lotions for their antipruritic effect. They also may be increased or decreased. Phenol should not exceed 2 per cent, and menthol should not exceed 0.5 per cent. Camphor and coal tar solution may be used in any strength desired. Solution of coal tar is especially useful on the thickened skin of chronic eczema.

Pastes. Pastes are composed of an ointment base, plus a large proportion of powder such as zinc oxide, starch and talcum. They are somewhat similar to ointments but are much thicker and stiffer. The best known paste is the zinc oxide paste of the N. F., commonly called Lassar's paste. This is made both with and without 1 per cent of salicylic acid. It is usually prescribed without the salicylic acid, but there is little choice.

Pastes may be employed on surfaces that have just stopped oozing or appear to be about to ooze. In this situation, a paste is safer to use than

	Powdery Lotions	*gm. or ml.*
No. 1.	Calamine lotion, N.F.	
No. 2.	Phenolated calamine lotion, N.F.	
No. 3.	Phenolated neo-calamine lotion, N.F.	*gm. or ml.*
No. 4.	Zinc oxide	15.0
	Glycerin	10.0
	Lime water	
	Water āā to make	120.0
No. 5.	Phenol	1.0
	Zinc oxide	15.0
	Glycerin	10.0
	Water to make	120.0

	Oily Lotions	*gm. or ml.*
No. 1.	Zinc oxide	15.0
	Olive oil	
	Lime water āā to make	120.0
No. 2.	Phenol	1.5
	Menthol	0.5
	Zinc oxide	15.0
	Glycerin	6.0
	Tragacanth	0.8
	Olive oil	30.0
	Lime water to make	120.0

	Clear Lotions	*gm. or ml.*
No. 1.	Menthol	0.5
	Tragacanth	2.0
	Glycerin	5.0
	Alcohol	40.0
	Water to make	120.0
No. 2.	Glycerin	3.0
	Tragacanth	5.0
	Water to make	120.0
No. 3.	Phenol	1.0
	Menthol	0.5
	Glycerin	10.0
	Alcohol, 50%, to make	120.0
No. 4.	Phenol	1.5
	Salicylic acid	2.0
	Glycerin	5.0
	Camphor water	60.0
	Alcohol to make	120.0
No. 5.	Solution of coal tar	10.0
	Glycerin	5.0
	Alcohol, 50%, to make	120.0

an ointment as the ointment is liable to increase the tendency toward oozing. The paste, being less greasy, has somewhat of a drying effect which is entirely lacking in the ointment. Almost any desired drug may be incorporated in the pastes.

When using a paste, the skin should be well covered with it, and the paste renewed twice a day. If the paste is to be covered with a dressing, a smooth layer of absorbent cotton should be applied directly over the paste and held in position by a bandage. If gauze or cloth is used to cover the paste, the grease will come through the meshes. It is neither necessary nor desirable to remove the old paste entirely when changing the dressing. Paste is very adherent, and too much rubbing in order to remove it thoroughly will produce itching. Remove only as much as will come off with gentle rubbing, and apply the fresh coating over what remains of the old. When it is desired to remove a very adherent paste this should be done with the aid of light mineral oil. Benzene will remove paste and ointment very readily, and if not used too often will do no harm.

	Formulas for Pastes	*gm. or ml.*
No. 1.	Paste of zinc oxide, N.F. (Lassar's paste)	
No. 2.	Coal tar	3.0
	Paste of zinc oxide to make	60.0
No. 3.	Liquid phenol	1.0
	Paste of zinc oxide to make	60.0

Ointments. These preparations are chiefly useful on dry, scaly and thickened skins. Under these conditions they are more effective than pastes or lotions. The base of the ointment is not important in spite of all that has been said about penetrability. The most widely used base is petrolatum, and there is no choice between the white and the yellow. Petrolatum is often combined with lanolin, wax and other substances to change its consistency. The white ointment and the yellow ointment of the U.S.P. are good bases.

	Ointments	*gm. or ml.*
No. 1.	Zinc oxide ointment	
	Boric acid ointment āā to make	30.0
No. 2.	Liquid phenol	0.5
	Zinc oxide ointment	
	Boric acid ointment āā to make	30.0
No. 3.	Liquid phenol	0.5
	Menthol	0.1
	Starch	5.0
	Zinc oxide ointment to make	30.0
No. 4.	Rose water ointment, U.S.P.	
No. 5.	Ammoniated mercury	1.0
	Rose water ointment, U.S.P., to make	30.0
No. 6.	Ammoniated mercury ointment, U.S.P. 5%	
No. 7.	Coal tar	2.0
	Zinc oxide	5.0
	Starch	5.0
	Petrolatum to make	30.0

Phenol, menthol and camphor may be added to any ointment for the antipruritic effect. Phenol should not exceed 2 per cent, and the menthol should not exceed 1 per cent. Camphor may be used up to 10 per cent. The rose water ointment (cold cream) of the U.S.P. is a very soothing, softening, and cooling base. It may be used alone or with the addition of phenol and menthol. With the addition of ammoniated mercury, the rose water ointment will be helpful in the presence of secondary infection.

Sulfonamide ointments should be avoided if possible on account of the danger of sensitization. If a purulent eruption cannot be controlled by other means, a 5 per cent sulfathiazole ointment may be tried. It is rarely necessary to resort to this.

Roentgen Ray Treatment of Dermatitis

While the roentgen ray treatment of dermatitis is widely employed and is very helpful at times, it must be used with great caution. It should only be done by an experienced radiologist or dermatologist, and too much must not be expected of it. The chief danger is too continuous use. Not more than four or five exposures should be given in a series, and the series should not be repeated too soon nor too often. Unless there is reasonably prompt benefit from roentgen ray, it should be abandoned at once. It is most dangerous to persist in using it in the hope of ultimate benefit unless there is definite evidence of good effect. It is used in all types of eczema. It is least effective in the erythematous type and most effective in the chronic cases. It is often very useful in the relief of itching.

18. *Other Allergic Dermatoses*

ROBERT A. COOKE

IN ADDITION to the several types of allergic dermatitis there are a number of manifestations of the skin classed as dermatoses, some of them well recognized and accepted as allergies, and others up to the present time not usually included in the group of allergic diseases. Certain of these, as urticaria and angioedema, are relatively common. The reason for including the entire group in this chapter is because of their frequent clinical association and the relationship of their immunologic and histologic reactions.

Urticaria

This lesion of the skin, known to the laity as hives or nettle rash, is characterized by erythema, whealing and itching. It may occur as an isolated acute attack, or it may recur at longer or shorter intervals, or it may be chronic. Ordinarily regarded as a trivial affair, urticaria of the recurring or chronic type may be of serious concern to the patient and baffling to the physician, as an etiologic diagnosis is often difficult and the treatment, therefore, is not effective.

Urticaria as a Disease of Allergy. In the early use of diphtheria antitoxin the urticarial lesions of serum disease appeared about ten days after the injection of the serum in about 10 to 12 per cent of the patients given these parenteral injections of horse serum. Later, with the use of large doses (100 ml.) of antipneumococcus serum, the incidence of serum disease rose to approximately 90 per cent.[1] The studies of anaphylaxis and serum disease and serum shock soon supported the idea that urticaria was an antigen-antibody reaction, and hence an allergy (Chapter 2, p. 29).

In the studies on heredity by Cooke and Vander Veer[2] and Cooke and Spain[3] urticaria appeared in patients and antecedents of patients with asthma and hay fever too often to be entirely disregarded as a possible related allergy. The clinical studies of Menagh[4] (260 cases), of Rackemann[5] and of Fink and Gay[6] give 32.6 per cent, 22 per cent and 28 per cent respectively as the incidence of familial allergy in urticaria patients, while a personal allergy other than urticaria was found by Menagh in 30 per cent, and by Fink and Gay in but 15 per cent, of their group of 170 patients. Urticaria is also a common symptom of the constitutional or systemic reaction due to an overdose of pollen allergen in hay fever therapy. It is very rare as a spontaneous symptom of pollen allergy, apparently because pollen is not absorbed from the air in a quantity sufficient to reach the sensitized cells from the blood, and under usual conditions is not absorbed through the skin.

Finally, it is possible to prove in the case of the acute urticarias of the "immediate" type due to foods that the skin-sensitizing antibody is present in the skin and blood. Positive direct and passive transfer tests furnish this evidence.

For these reasons, urticaria is generally regarded as one of the diseases of allergy, but it is not possible to assert that all urticarias are based upon an antigen-antibody reaction, for such proof is not yet at hand. However, in view of the various types of allergy recognized (see Chapter 2), this is a tenable hypothesis on which to work.

Origin of the Wheal. Many theories have been advanced to account for the wheal which is the characteristic lesion. It has been ascribed to a spasm of the blood vessels in a circumscribed area followed by a dilatation of the arterioles with exudation of serum. Finally the pressure of fluid forces out the blood and produces the blanched wheal. Gilchrist[7] believed there is an inflammation of the derma caused by an escape of toxin from the blood. The wheal, however, is due to the resulting serous exudate.

More recently the theories of Lewis[8] have prevailed. As a result of his work he believed in a local reflex through the terminals of sensory nerves due to released H-substance (histamine), which dilates the arterioles and produces the flare. The action of histamine on the capillary wall affects permeability with the resulting edema and wheal. While it is true that histamine injected into the skin produces a typical wheal, the proof of its local production in urticaria is lacking. It is fair to assume, however, that some substance is formed as a result of the sensitized cell-allergen union which induces vascular dilatation and serum osmosis to produce the allergic wheal. If there are non-allergic wheals they may be due to the same or a different substance. All that is really known is the superficial fact that each wheal is a strictly localized vasomotor storm.

Etiology. If one scans a number of textbooks, especially the older ones, one finds that the list of causes of urticaria is very long and varied. In view of our present knowledge of allergy I shall list those that appear to produce an effect based on allergy, and those that directly at least. are not allergic, if they are basic causes at all.

1. Based on Allergy.
   - Infection:—Bacterial infections (virus?)
     - Protozoan—Plasmodia of malaria
     - Metazoan—Cestode (Tapeworm)
       - Nematode (Roundworms)
       - Arthropods—Scabies, pediculosis, insect bites—mosquito, spider, ticks, bees and bedbugs

    - Ingestion:—Foods and drugs
    - Inhalation:—Pollens, dust, odors
    - Injection:—Drugs and other biologicals, serums, liver, insulin, endocrines such as diethylstilbestrol, and vitamins
    - External contactants
    - Physical agents
2. Non-Allergic causes.
    - Dyspepsia—constipation
    - Pregnancy
    - Endocrine dyscrasia
    - Psychogenic factors

1. Causes Based on Allergy. INFECTIONS. Protozoan and metazoan and dermatomycotic infections of man are known to produce clinical urticaria, and allergy is known to exist in many of these infections. Eyermann and Strauss[9] reviewed the literature on allergy in malaria in their report of a case.

Cestode infestation is accompanied by blood eosinophilia.[10] Rupture of an hydatid cyst is known to produce urticaria, and on this is based the Casoni skin test with hydatid fluid for diagnostic purposes.

Nematodes are equally active in producing blood eosinophilia and are factors in allergic disease including urticaria. Ascaris infestation has been studied by many.[10, 11, 12, 13] Asthma due to ascaris[14] has been reported and positive skin tests and systemic reactions were obtained with extracts. However, clinical cases of urticaria due to ascaris are rare.

Infection with Trichinella spiralis frequently produces a sensitization on which the diagnostic test with trichinella extract is based. However, infection with this nematode is not considered an important factor in clinical urticaria.

Arthropods responsible for scabies and pediculosis, as well as the mosquito, spider, bee, bedbug and tick, all produce an urticarial type of lesion with their bite or sting and are reported as causative agents.[15, 16, 17, 18] Whether these are antigen-antibody reactions or are due to a direct toxic action is not positively known, but bee sting is certainly capable of producing severe allergic shock in sensitized persons, with edema, urticaria, asthma and collapse. In other cases the reaction is localized but presents an extreme degree of edema.

Dermatomycetes (fungus) Infection also stimulates the immediate wheal type reaction to extracts as well as the delayed tuberculin type of allergic response so well demonstrated by Sulzberger and his associates.[19]

In general it may be said that all such agents are uncommon causes of persistent or recurring urticaria but they should be kept in mind in the many problem cases.

Bacterial Infections. As causes of cutaneous edemas these rank high. The published reports do not separate urticaria and angioedema. In the series of Fink and Gay,[6] infection was a cause in 30 per cent, and in the main was focal, in tonsils, sinuses and teeth. Menagh,[4] in his report some years ago, stressed the importance of infection of the biliary tract as determined by transduodenal drainage and cultures. My own experience supports the etiologic importance of focal infection in both urticaria and angioedema. The oral and upper respiratory tracts are usually the seats of such foci, but one cannot disregard the probable importance of biliary or intestinal infection though the evidence is not entirely convincing. Any focal infection, however, may be a cause, especially a suppurative one. In one of my patients, referred to me because of urticaria of three years' duration, the diagnostic study was interrupted by what appeared to be an unrelated illness characterized by pain in the anal region. This was found to be due to a perineal abscess originating in the scar of a repair operation done five years earlier. The abscess was opened, and two ounces of pus removed. By the next day urticaria had practically disappeared and has never returned. Staphylococcus aureus and hemolytic Escherichia coli were cultured from the pus. However, the focal area need not be suppurative nor as extensive as in this case. I have known a persistent urticaria to disappear after the removal of a single tooth with a small granuloma at the apex. The organisms usually found in the focal areas and considered as causes are those of the staphylococcus and streptococcus groups, the pneumococci, and the colon group of bacteria, especially the hemolytic type.

INGESTED SUBSTANCES. Foods and Drugs. Foods are important if one considers the sum total of all urticaria cases, but in a large percentage of these the diagnosis is made by the patients themselves on the basis of an immediate reaction to a particular food, hence they are not real diagnostic problems. The cases of urticaria which represent "delayed reactions" to foods are difficult to diagnose and to prove, as the skin tests are negative. This has been previously explained with case citation (see Chapter 2, page 27).

Any food is a possible factor in an individual case. I have seen urticaria caused by mushroom, artichoke, radish, corn meal, and alligator pear, but the following foods because they are habitually eaten may be listed as chiefly responsible:

Egg white
Chicken
Chicken broth
Fish and shellfish
Milk
Pork (Lard)
Lamb
Veal
Wheat
Buckwheat
Tomato
Potato
Celery
Peas
Strawberry
Cantaloupe
Orange
Chocolate
Nuts
Honey
Beer
Mustard
Soy bean
Cottonseed oil

Among these foods it is difficult to say which is the most important, or to grade them as to their relative frequency in producing reactions.

Certainly milk, egg, shellfish and fish stand high on the list. Honey is an important factor but it is not the honey per se, but the pollens from which honey is made. Buckwheat honey is an allergen to those sensitive to buckwheat. Some years ago I saw a patient made violently ill with honey made from gladioli by the bees. Both urticaria and asthma were severe in this acute case.

Among drugs, those chiefly responsible are:

Acetylsalicylate (Aspirin)
Quinine
Coal tar products
Barbiturates
Iodides
Opium and its derivatives
Sulfonamides
Arsenicals
Bismuth

INHALED SUBSTANCES. Air-borne allergens acting after inhalation barely deserve practical consideration, for if they were important the patients sensitive to pollens and to danders or any other inhalant allergen ought to have urticaria as a part of the clinical picture of hay fever or asthma, and that rarely occurs.

The recent report by Johnson and Alexander[20] that ragweed pollen antigen is present in the serum of normal persons as well as hay fever patients during the pollinating season contraverts this theoretical conception as to why urticaria is not a common manifestation of hay fever. However, the absorption of unaltered antigen after inhalation, ingestion or injection has been shown by many workers to cause reactions in skin sites on normal subjects sensitized with appropriate serums. Why a wheal should appear under these circumstances, yet does not occur during the pollinating season in hay fever patients, creates a problem that can be resolved only with further study.

EXTERNAL CONTACTS. The usual inhalant substances may act by contact with the external skin when the contact is intimate, and cases of urticaria do occur from silk, house dust, feathers, pyrethrum, wool, the saliva or dander of animals, and from cosmetic or toilet preparations containing cottonseed oil, lanolin and orris root.

INJECTED DRUGS AND THERAPEUTIC AGENTS. This group includes the drugs previously listed, when parenterally introduced, as well as therapeutic serums, liver extracts, insulin, vitamin preparations, especially thiamine chloride, and endocrine substances, as diethylstilbestrol. Pollen extracts should be included on account of their extensive use and the not infrequent systemic reaction with urticaria promptly following an injection.

PHYSICAL AGENTS. Urticaria may be produced by physical agents, which however are not important etiologic factors. Heat and light rays may cause urticaria, but cold is the commonest agent. The edema occurs only at the point of contact.

Mechanical irritation may produce a wheal. This occurs to a slight degree in normal skin. When a light stroke or a scratch of the skin produces a "definite" wheal with bordering erythema the condition is spoken of as urticaria factitia or dermographism. It may be very annoying when present in marked degree, as the lesions are accompanied by itching and burning. It may occur not only on the skin but may involve the mucous membranes of the mouth and pharynx. Such cases are not confused with clinical urticaria, but the wheals produced appear to be of the same general nature.

In most cases the patient is aware of the cause, and physical allergy is not usually a diagnostic problem (see Chapter 30).

2. *Non-Allergic Factors in Urticaria.* There are a number of causes generally stated as responsible for urticarial reactions. These include psychogenic factors, fatigue, constipation, indigestion, endocrine dyscrasia, menses and pregnancy. With regard to all of these it is difficult to establish proof of their etiologic importance. My feeling is that, just as in asthma, these are contributing, exciting, or perhaps predisposing and modifying factors, but not of basic importance in producing urticaria and edema. (See comments on non-specific factors in Appendix, page 547.)

Summary. Of the cases which present themselves for an etiologic diagnosis 35 per cent are due to infection, usually focal, 10 per cent are caused by foods and another 10 per cent by drugs. This leaves nearly half of our cases etiologically undiagnosed. This does not take any account of the considerable group, usually with acute urticaria, who are able to diagnose the cause themselves because of the immediateness with which the reaction occurs following some special food, drug or external contact.

Immunologic Considerations. Mention has been made of the *immediate* and *delayed* type of reaction (Chapter 2). The former is characterized by the immediate clinical reaction following contact with the allergen. If the allergen is injected it may be within seconds or minutes, and if ingested it usually is within one hour. Except for non-protein drugs, the skin test is immediately positive and passive transfer is effected. This type of reaction is common with ingested foods and some drugs, with externally contacted substances, and injected biological products.

The delayed reaction occurs from two to forty-eight or even seventy-two hours after contact. Skin tests are negative by direct and passive transfer methods. A characteristic of this reaction is the *fixation of the incubation period* for any particular substance in the particular patient. The allergens in these urticarial reactions are foods, drugs, and the bacterial substances.

A possible hypothesis which I[21] offered some years ago in explanation for the late food reactions is that they represent a response to certain split products of the food, and the incubation period represents the time needed by the body to digest the substances to the reactive allergen stage.

Pathology. In urticaria and angioedema the tissue change is a functional and reversible one. In urticaria the lesion occurs in the upper papillary layer of the cutis, while in angioedema the reaction occurs in the deeper or subcutaneous tissue, hence the more extensive and less circumscribed area of edema. The local exudation of serum into the tissues is the main characteristic. Leukocytes and round cells are present with few if any eosinophils.

The usual absence of blood and tissue eosinophilia in urticaria that is not associated with other allergies as rhinitis and asthma is not at present explainable. Certain it is that eosinophilia is not typical of urticaria from any cause.

Symptomatology. Urticaria varies from the very acute to the very chronic. *Acute urticaria* is sudden in onset. Generally the lesions are widely disseminated over the body, profuse, and may coalesce into broad areas of superficial edema with defined borders. Erythema and pruritus are intense. Such outbursts are usually limited to a relatively few days. Many of these cases represent immediate reactions to food allergens known to the patient but taken accidentally. In such patients there is often an acute gastro-enteritis with vomiting and diarrhea due to the mucosal reaction of the stomach and intestines.

During the attack the individual wheal suddenly and spontaneously disappears while new wheals continue to develop. Intense pruritus usually precedes the wheal in any spot and may disappear as the wheal develops. Occasionally pruritus may be absent. Typical dermographism is not commonly associated with urticaria, nor is angioedema.

Chronic Urticaria. In this clinical form the lesions are less fulminating and more sparse, though they may appear from time to time over any portion of the body. These patients frequently have more trouble in the late afternoon or on retiring, while during the day they may be quite free from symptoms. The attacks last for weeks, months and even years. In these cases the wheals may be of the typical blanched variety, but many modifications are seen and described by such terms as pigmented and hemorrhagic or papular urticaria. The irregular but spontaneous appearance and disappearance of any attack makes a definite and proven diagnosis extremely difficult. Associated conditions are frequently seen, since many of these cases are due to infective foci which contribute to symptoms such as fever, fatigue, headache, indigestion, diarrhea and arthritis, and to such other evidences of disease as anemia, uric acid retention, hyper- or hypothyroid activity, and increased or decreased blood pressure.

Differential Diagnosis. As a rule a diagnosis of urticaria is easy, but one should be aware that insect bites such as those of the bedbug and mosquito may simulate the reactions, but are differentiated by the pinpoint bite at the center of the lesion. The lesions of pediculosis and scabies are characteristic aside from the urticarial wheal they may cause, and are indicated by the scratch marks the parasites or their eggs deposit.

More important and more difficult to differentiate are the lesions of the erythema group. In the latter, pruritus is not a feature; the individual lesion is more persistent and painful. If the lesion promptly disappears after the injection of 0.5 ml. of epinephrine 1:1000 there is little doubt of the diagnosis of urticaria.

Etiologic Diagnosis. This is based on (1) history, (2) physical examination, (3) skin tests and (4) the clinical procedure of trial and error.

(*1*) *History.* In the history one looks for family or personal allergies, past or present. The patient's external contacts are relatively unimportant.

Of real significance may be the dietetic habits and use of any drugs as cathartics, sedatives, vitamins and endocrine products, or aspirin and other analgesics. As to the use of foods one should inquire particularly regarding any unusual food eaten or any food taken to excess prior to the onset, especially those taken uncooked.

In urticaria the quantitative food factor may be important, as illustrated by one of my patients with urticaria of several months' duration. I saw her at the hospital on her tenth postpartum day. Urticaria was acute, general and distressing. She had never had such trouble before, and was eating nothing she had not taken all her life. The story was brought out that in the latter months of her pregnancy she had drunk two quarts of milk a day. This was the only unusual factor in the history, for ordinarily she did not take milk except in the preparation of foods. With the avoidance of milk the urticaria rapidly disappeared. The skin test to milk was negative. She has never had any return of trouble though using milk in the customary amounts in cooked foods.

The history of an attack may give clues, and one should inquire as to the onset, course, duration and character of each of the attacks, and its relation to eating, to constipation, to fatigue and to the use of medicaments. The relation of an attack to acute infection or to evidences of chronic infection must be sought for, as infection is one of the commonest known causes.

(2) *Physical Examination.* This must be complete and careful in order to discover the general state of health of the patient, and *particularly* the evidences of focal infections. Most of the primary focal infections involve tonsils, sinuses, ears and teeth, but they may be found in the gallbladder, the appendix or the genito-urinary tract. Appropriate roentgenologic, bacteriologic and other laboratory examinations must be made to assist or support the physical examination.

(3) *Skin Tests.* When positive, urticaria is a reaction of the "*immediate*" type, and the allergen is usually known to the patient whose story is merely verified by the physician by means of a skin test. Such cases are usually of little significance as the reacting food is regularly avoided though occasionally taken by mistake.

Patients do not consult physicians for urticaria of known cause, but only when the cause cannot be fathomed, as in "delayed" allergy. In obscure cases skin tests may be done with a few inhalants such as dust, feathers, silk, wool, danders, and possibly with those foods listed as causes under Etiology, but in any case of a positive skin test care must be taken to prove the clinical import of the skin reaction.

(4) *Clinical Trial and Error Procedure.* External contacts are not really important, but any that are under suspicion, as silk or wool, should be avoided.

DRUGS. These should be avoided completely and long enough, at least two weeks, to establish any causal relationship. There is no other way to test satisfactorily for drug allergy.

FOODS. Any form of restrictive diet is satisfactory if the history indicates the possible significance of any particular food. Those foods listed as common causes might well be eliminated, and any food being taken in unusual amounts must be avoided. A simple method is to have the patient keep a diary and chart the foods eaten as well as the amount of urticaria present. If any food is definitely suspected its complete withdrawal should be promptly followed by relief, and its resumption must again produce the attack. This procedure is not easy, and often fruitless.

INFECTIONS. The only satisfactory evidence of bacterial factors is the disappearance of symptoms following the elimination of foci. Autogenous vaccines may be made, and with their use occasionally a symptomatic reaction is obtained, but if a long-standing urticaria responds promptly to the complete removal of any one or several foci, further proof is usually not required. Skin tests with such vaccines are useless.

Summary. Many cases of urticaria are etiologically diagnosed by the patient and do not require the physician's assistance. Those that do present themselves are almost always negative to skin test; they represent the delayed type of reaction.

The commonest known causes of urticaria are infections, usually focal, and ingested foods and drugs. Of the cases presenting themselves for diagnosis, not over half are satisfactorily solved.

The history, physical examination and clinical method of avoidance and use offer the best approaches to the diagnosis of the cause.

In all cases in which the cause is found and removed there is a fairly prompt disappearance of the lesion within a few days. That is, if an offending allergen is removed the urticaria does not and cannot persist.

Treatment. *Symptomatic.* Subcutaneous injection of epinephrine (1:1000) 0.5 ml., or epinephrine in oil 1.0 ml., or ephedrine $\frac{3}{8}$ grain (0.024 gm.) by mouth, may be repeated from time to time as indicated, and will temporarily relieve the eruption and the itching.

Benadryl (Parke, Davis) or pyribenzamine (Ciba) in doses of 50 mg. three times a day may be used orally for relief and is successful in many of the acute cases. The relief is fairly prompt but of relatively short duration. They are both new drugs and their uses and limitations are not fully defined. A synthetic vitamin K, menadione (Winthrop), has been used by Black[22] for the treatment of urticaria. Two milligrams were given orally three times a day. Seventy eight per cent of the patients with a prolonged prothrombin time were benefited as compared to 32.5 per cent with a normal prothrombin time. Adequate confirmation is not yet forthcoming.

General. In an *acute* case immediately following the ingestion of a known reacting food or drug, an emetic or gastric lavage may help to remove the active agent. These cases are rarely seen early enough for such measures. If seen several hours after ingestion, catharsis, colonic irrigation and abundant fluids in large amounts by mouth promote allergen elimination.

In the *chronic* cases eliminative measures may help somewhat. Fluids should be forced and nothing but fluids given for the first twenty-four hours. At night, to induce rest, a mild sedative of bromide 15 grains (0.97 gm.), or chloral hydrate 10 grains (0.65 gm.), or phenobarbital 1 grain (0.06 gm.), may be used if these drugs are not under suspicion from previous use. If the attacks usually occur at night epinephrine in oil 1 ml. by injection, or ephedrine $\frac{3}{8}$ grains (0.024 gm.) in enteric coated tablets, may be used at bedtime.

Local applications of calamine with phenol may be tried, but as a rule they are of little help. Tepid starch or soda baths sometimes give relief.

The diet should be light, avoiding those foods mentioned as frequent causes, as well as all highly seasoned and rich foods and alcohol.

Specific Therapy. This is based upon a successful and proven diagnostic study and may be summed up simply as removal or avoidance of the cause. In the case of drugs and external contacts this is simple. In the case of foods it is easy to avoid most of them. When milk, egg or wheat is the agent there is some temporary difficulty, for they should be completely avoided for a period of a week or ten days. However, since a quantitative factor is involved there is usually a probability that even these foods may be used within limits sufficient to ease the strain of strict dietetic regulations, especially if taken in well-cooked form. The use of food allergens for immunization therapy is rarely indicated.

In case of infective foci, prompt measures should be taken for surgical intervention, or for treatment if the focus is not removable. Vaccine therapy may be of help when foci are not susceptible to complete or partial surgical treatment. Fink and Gay[6] report 74 per cent of twenty patients as cured by vaccine therapy. Best results are obtained in my hands with autogenous culture vaccines. Some such schedule as the following may be used, giving subcutaneous injections of vaccine (heat-killed) at five- to seven-day intervals up to the maximum dose which may then be given at two-week intervals for 6 to 8 additional doses and continued monthly if necessary.

Vaccine 0.01% by Volume		*Vaccine 0.1% by Volume*		*Vaccine 1% by Volume*	
Dose	Amount	Dose	Amount	Dose	Amount
1.	0.1 ml.	5.	0.1 ml.	10.	0.1 ml.
2.	0.3 ml.	6.	0.2 ml.	11.	0.2 ml.
3.	0.5 ml.	7.	0.4 ml.	12.	0.3 ml.
4.	0.7 ml.	8.	0.6 ml.	13.	0.4 ml.
		9.	0.8 ml.	14.	0.5 ml.

All patients will not tolerate these doses. In case there is a local reaction lasting over thirty-six hours, that dose should be repeated or possibly reduced and the gradual increase resumed when the injections are again tolerated.

If a symptomatic (urticarial) reaction develops 12 to 36 hours after an injection, the dose will again have to be modified to suit the particular patient.

Treatment with histamine, histaminase, hapamine, calcium, peptone, ethylene disulfonate (allergosil) and many similar suggested remedies has not proven beneficial in my clinic. Such measures as autoserotherapy and ultraviolet irradiation of blood have been found useless. The occasional satisfactory results reported from the use of these drugs or procedures are typical examples of fortuitous coincidences attending the treatment of a disease characterized by a fluctuating and unpredictable course.

Angioedema

(Quincke's Disease, Giant Urticaria, Angioneurotic Edema)

I shall use the contracted term angioedema instead of the usual angioneurotic edema, because it is simpler and because the component "neurotic" is of doubtful significance in view of the present conception of an allergic basis for this dermatosis. While it is true that the allergic mechanism is not known, there are certain facts supporting an hypothesis of allergy, such as the occasional association of this condition with other allergies, the virtual identity of the causative agents with those of urticaria, and the similarity of response in those cases in which the exciting agent has been found.

In angioedema the lesion originates in the deeper subcutaneous tissues of the skin, hence the edema is greater and the individual lesion is less circumscribed and defined than in urticaria. Itching is not as pronounced as in urticaria. Patients frequently describe the lesions as stinging or burning, and often there are no subjective symptoms other than those produced by the swelling.

Although urticaria and angioedema are usually linked together and so described, actually the combination of the two lesions is rarely seen in any patient at one and the same time, or indeed at different times.

Historical Background. Angioedema was named for Quincke after his description of the disease in 1882,[23] though it was described earlier by Milton.[24] Osler[25] described the hereditary type occurring in five generations. Phillips and Borrows[26] have collected other cases from the literature, and Phillips[27] has also reported it in dogs. The majority of cases, however, are not of this hereditary type, but occur sporadically and often with no familial or other personal allergies.

Etiology. The specific excitants of angioedema are in general those of urticaria—bacterial infections, foods and drugs. Most authors include psychogenic and endocrine factors. The illustrative case reports of such agents are by no means convincing and are not susceptible of proof. The cases that fall in these latter groups I prefer to regard as undiagnosed from the standpoint of specific causes.

The percentage of these cases definitely diagnosed as to cause is not over 50 per cent. In the diagnosed group, infection is even more important than it is in urticaria.

Immunology. Rarely does one see an acute immediate reaction such as so commonly occurs in urticaria from foods or drugs; therefore, a positive skin test with etiologic significance is likewise rare. By the same token passive transfer tests are also negative. Practically all of those cases in which a diagnosis has been made represent the delayed type of reaction to foods, to drugs or to infective agents.

Symptomatology. Although cases do occur in childhood, by and large angioedema is an affliction of adult life. The youngest patient I have seen was a baby two years old, in whom it was in association with cyclic vomiting. The visible edemas were of the face, hands and feet. Another, a boy five years old, had recurring attacks of edema in the right cheek for two years. By avoiding milk the attacks were stopped. He could tolerate one glass of milk a day, but if he drank a quart of milk the swelling always returned after six to eight hours.

The symptoms of angioedema vary, depending on the location of the swelling. This may occur anywhere, but the sites of predilection are the eyes, lips, hands and feet, and the tongue and glottis. It is because of glottic swelling that angioedema may be a serious disease, especially the hereditary type, as shown by Crowder and Crowder.[28] The swellings last for one, two and even four days, disappearing gradually. As a rule they are not favorably affected by epinephrine or ephedrine. Attacks of edema occur with great irregularity, and for this reason credit is often given undeservedly to the therapeutic measures or the diets advised.

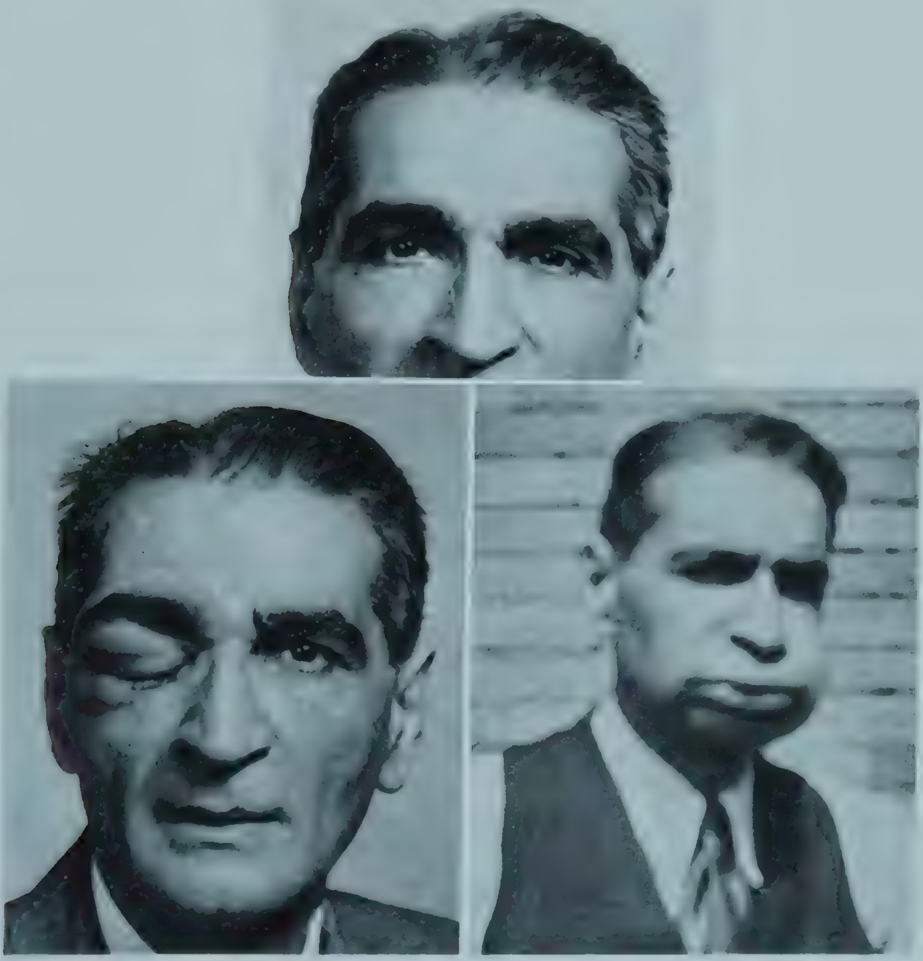

Fig. 27.—Angioedema—typical example. Cause undetermined. This patient never had urticarial manifestations.

Angioedema is characterized by the frequency with which esophageal, gastro-intestinal (Chap. 23), or neurologic (Chap. 19) manifestations occur, with cutaneous lesions but frequently without them. The gastro-intestinal symptom is usually pain rather than the prompt vomiting and diarrhea associated with urticaria.

Diagnosis. The diagnostic methods given under Urticaria are entirely applicable here in every detail. Skin tests are rarely of any value. Eosinophilia is very uncommon. The history, physical examination, with attention to foci of infection, and restrictive diets may afford an answer. All drugs must be eliminated. In all cases one should attempt to prove the correctness of diagnosis and not assume it on the basis of a fortunate coincidence.

Treatment. Since the correct diagnosis is not too frequently made, treatment is correspondingly ineffective.

Symptomatic treatment with epinephrine and ephedrine may be tried but is not particularly successful. When the tongue, pharynx or glottis is involved these patients should be temporarily hospitalized so that tracheotomy may be done promptly if indicated.

Non-specific therapy with histamine, histaminase and hapamine has been useless, in my hands. The same may be said of calcium and peptone injections, autoserotherapy and similar procedures.

The Purpura Group

In general the purpuras are divided into two main types, the non-thrombopenic and the thrombopenic, the essential differentiating factor being indicated by the name. It is not the purpose here to deal extensively with the entire clinical and pathologic features of the purpuras, but to bring out the established relation of both of these conditions to allergy. This does not mean to imply that allergy is the explanation for all purpuras, but merely that certain cases of both types have complied with our concepts of allergic reactions.

Non-thrombopenic purpura is frequently associated with joint lesions—Schönlein's disease—or with gastro-intestinal symptoms—Henoch's disease. The attacks of purpura are frequently recurring and in general are mild.

Thrombopenic purpura (purpura hemorrhagica or Werlhof's disease) is a more serious condition occurring in acute or chronic form, and not infrequently has a fatal termination.

Osler,[29, 30, 31] in a series of papers from 1895 to 1914, presented as he called them "a motley group of cases, some of purpura, some of angioneuroticoedema, others of peliosis rheumatica; others, again of exudative erythema." The fact is that any case may show any one or several of these lesions at the same or different times while exhibiting as associated conditions gastro-intestinal, renal and arthritic complications. In his last paper in 1914,[31] when anaphylaxis was coming under consideration as a possible explanation for disease, Osler commented on its possibility as a common denominator in explanation of his "motley group" of diseases. Alexander and Eyermann[32] in 1927 reported three cases of food allergy in Henoch's purpura and since then many cases have been reported. Hampton[33] reporting two cases reviewed the literature up to 1941.

The basis for allergy as an explanation for the disease lies in the frequency of familial and personal allergy, and the reproduction of the symptoms at will following the administration of the causal agent.

Etiology. For our present purposes no distinction need be made as to whether the platelet count is normal or low, for reported cases appear to fall into both groups, although the non-thrombopenic type is more common.

Foods. Milk, egg white, egg yolk, chicken, lamb, pork, beef, wheat, potato, anchovy, onion, carrot, plums and strawberry have been the allergens in the reported cases. There is no known reason why any food could not be the cause,

Drugs. Arsphenamine, bismarsen, sedormid, nervinal, quinine, ergot, amidopyrine, gold and iodides have been recorded as responsible for the hemorrhagic lesions.

Infection. All authorities agree that infection is an important factor, especially when there is an existing focus. These cases are hard to prove by provoking an attack as it is possible to do with foods and drugs. Purpura has been reported to have occurred in three patients following pertussis vaccine (Kugelmass[34]), and after a tuberculin test (Wright and Bacal[35]). I can recall cases in children when purpura appeared two to three days after tonsillectomy. However one may feel about it, the case for bacterial allergy in purpura has not yet received any very definite or final proof.

Immunology. The recorded cases due to food allergy largely represent the "delayed allergy" type with negative skin tests, although Alexander and Eyermann[32] and Barthelme[36] have each recorded a case with symptoms to an allergen giving an immediate wheal reaction. From our present knowledge of drug allergy, positive skin tests would not be expected. Tests with bacterial products or vaccines have yielded no information.

Symptomatology. The purpuras are seen in children and in early adult life. There may be no lesion other than purpura, or articular or visceral symptoms may occur as well as other cutaneous lesions. There may be fever and malaise. Hemorrhage may occur from the mouth, intestine, kidney or bladder. If bleeding is severe there may be anemia. Eosinophilia is usually absent, but was recorded up to 14 per cent in one of Hampton's cases with eosinophils present in the mucus of the feces.

Diagnosis. If there is reason to suspect allergy, all drugs must be withdrawn, and the patient put upon a diet avoiding at least milk, egg and wheat, or any other food indicated by a careful history. By clinical method of trial and error the cause may be determined, but no case should be reported as definitely proven until symptoms have been reproduced after the same time interval on three separate occasions under identical conditions. With suspected drugs the same procedure is followed.

Intradermal or scratch tests are not likely to be of help. A few tests with the more important allergens may be done. If definitely positive they at least indicate the allergic constitution of the patient, even though they may not be of etiologic significance.

Treatment. Aside from the usual medical care the treatment of a diagnosed allergic purpura consists of avoidance of the cause, be it food or drug. If infection is a presumed cause, the focus should be removed at the first opportune time, or treated, if not removable, with antibiotics or vaccine.

The Erythema Group

The erythema group of skin diseases is briefly presented in connection with diseases of allergy because of the possibility, or rather probability, that they represent several types of skin lesions resulting from allergic reactions.

This group of diseases comprises three types which differentiate themselves largely on the appearance of the lesion.

Erythema Simplex is evidenced by circumscribed areas of erythema of various sizes, or the erythema may be general and diffuse. The lesions are but little, if any, elevated, deep bluish red in color, and described as painful or burning by the patients.

The causes of erythema are many. External physical and chemical agents are numerous. More important are the rashes from drugs, as chloral, belladonna and salicylates, and those from foods, especially fish and shellfish. Still more significant are the cases associated with bacterial infection. As a matter of fact the erythema of scarlatina is a true but generalized erythema. A desquamation similar to that occurring after scarlet fever is seen in lesions from other causes if the inflammation is intense.

The histologic picture is one of inflammation of the corium, with exudation, vascular dilatation, and cellular infiltration by leukocytes, round cells and red blood cells. Eosinophile cells are not in evidence.

Erythema Nodosum. On account of the accompanying fever, malaise and polyarticular lesions, erythema nodosum is regarded as an evidence of infection. The skin lesions consist of slightly elevated nodules, dark red in color and painful to touch. As a rule they are symmetrically disposed over upper and lower extremities. Individual lesions last but a few days, appearing in crops from time to time. The disease runs its course in from a few days to a few weeks, and may be recurrent from year to year.

The cause is not definitely known, but generally the disease is regarded as an expression of bacterial infection—including rheumatic fever, tuberculosis, syphilis and gonorrhea. Lesions of this type are also recorded as due to drugs.

The histology is similar to simple erythema except that the more extreme extravasation of serum gives rise to the nodular swelling.

Erythema Multiforme. As its name implies, the lesions are extremely varied. They may be macules or larger areas of erythema, papules, nodes, vesicles, blebs which may be hemorrhagic, and rarely pustules. One type only, or several, or all varieties may be present at the same or different times. Usually the lesions are symmetrically distributed over the arms and back of the hands, legs and dorsum of the feet, the face and neck, rarely on the trunk.

The symptoms are those of the lesions described, often with mild or no constitutional disturbances. Muscle and joint pains may be present. The disease runs a course of several weeks, and is noted for its recurrences annually or several times a year.

The cause is unknown, that is, there is no specific etiology, but the disease is attributed to focal or systemic infections with any of the usual pathogenic organisms, including the tubercle bacillus. Drugs also have been cited as causes. I know of no case definitely proven in which food was the factor.

Allergic Basis. Osler[29, 30, 31] first called attention to the association of these various erythemas with urticaria, angioedema and purpura. The most diverse types of visceral disease were also encountered in his series of twenty-nine cases. Cerebral, gastro-intestinal and renal involvement, together with arthritis and hemorrhages from the mucous membranes, were recorded, and most interesting is the frequency with which any of the types of skin lesions appeared. On account of the clinical association of skin and visceral lesions Osler attributed them to a common source, and in his last contribution on the subject in 1914[31] he spoke of "anaphylaxis" as the key to the situation. As yet there is no proof, but the accumulating pathologic evidence of vascular lesions of hypersensitiveness and the association of the erythemas and purpuras with such known types of allergic responses as urticaria make the assumption of an allergic basis for the entire group not the least improbable.

Diagnosis. The clinical diagnosis is not, as a rule, difficult, whereas an etiologic diagnosis is rarely proven except by the subsequent course of events such as the interruption over a period of years of frequent recurring attacks. Whether the case be one exhibiting one of the forms of the erythema group or complicated with various edemas and purpuras and visceral lesions, one should always investigate the allergic background of the patient and his family, and consider the three main possible allergic factors of food, drugs and infection.

Treatment. This consists of avoidance if the cause is found to be food or drug. If infection may be a cause, discoverable foci should be removed or treated systemically with any of the indicated antibiotics and vaccines.

Local treatment consists in protection of lesions against trauma and infection.

Lupus Erythematosus

This disease generally involving the skin occurs as two types—the discoid or chronic, and the disseminated. Both are of unknown origin and there seems to be doubt as to whether the discoid ever passes over to the disseminated active form. Save for the typical butterfly rash over the nose and cheeks, these two conditions seem to have nothing in common unless both may be explained on a sensitization basis.

The Discoid Type is an extremely chronic disease of the skin with lesions of small elevated papules covered with a grayish scale. Over the course of years the lesion extends from its periphery and is characterized by the smooth depressed center of the central cicatrix. While the lesion bears no resemblance to the erythemas the following case suggests a sensitization reaction to bacterial infection.

G. G., a man, sixty-two years of age, was first seen by me in October 1934. Four years previous (1930), in the heat of summer, an erythema developed over the bridge of his nose and lasted two months. With cool weather the erythema gradually disappeared. The following summer the lesion again appeared and again cleared during the winter. During the ensuing summer the erythema reappeared on the nose and spread to the cheeks and ears, and was accompanied by constitutional symptoms of malaise and fever. This time the lesion did not entirely clear in winter though it was somewhat better. In July 1934 there had been a marked exacerbation of the lesion over the nose, cheeks, ears and lips, with considerable general edema of the entire face. This was the condition of the patient when I saw him in October 1934.

A physical examination revealed a man in good general health. The heart was enlarged in its transverse diameter with blood pressure 120/80, rate 80, and no evidence of failure. The lungs were normal. The examination of the abdomen and extremities showed no abnormalities. Nasal examination revealed extensive polyposis of the ethmoid sinuses. Dental examination showed advanced infection involving six teeth in the lower jaw. All the upper teeth had been removed. Examination of the heart with electrocardiogram, by Dr. Harold Pardee, showed "enlarged heart with myocardial fibrosis and degeneration, both being on an arteriosclerotic basis." The genitourinary tract was found free of infection, and normal save for a trace of albumin and a few hyaline casts in the urine. There was a blood eosinophilia of 10 per cent, otherwise the blood count was normal. Dermatologic consultation with Dr. Dudley Stetson confirmed the diagnosis of lupus erythematosus, discoid type.

Management. The infected teeth were removed. Later a polypectomy with exenteration of ethmoid cells was done by Dr. Clark Grove. This tissue yielded a pure culture of hemolytic Staphylococcus aureus.

An intradermal test was made with a 1:100 dilution of staphylococcus toxin filtrate obtained through the courtesy of Dr. Earl Burky. There was no immediate reaction, but twenty-four hours later there was a marked area of redness and edema covering the entire anterior forearm from elbow to wrist (Fig. 29). A control test with heated toxin in the same amount and dilution on the opposite arm gave an entirely comparable result. Many similar tests on various patients had shown either no reaction to these doses or had produced an area of 1 to 2 cm. diameter.

Course. Two months following the removal of infective foci the facial lesions were retrogressing rapidly. During the ensuing summer of 1935, the patient reported that the lesions had "completely vanished except for a small claret colored spot 1 cm. in diameter over the lower bridge of the nose. No new spots have appeared."

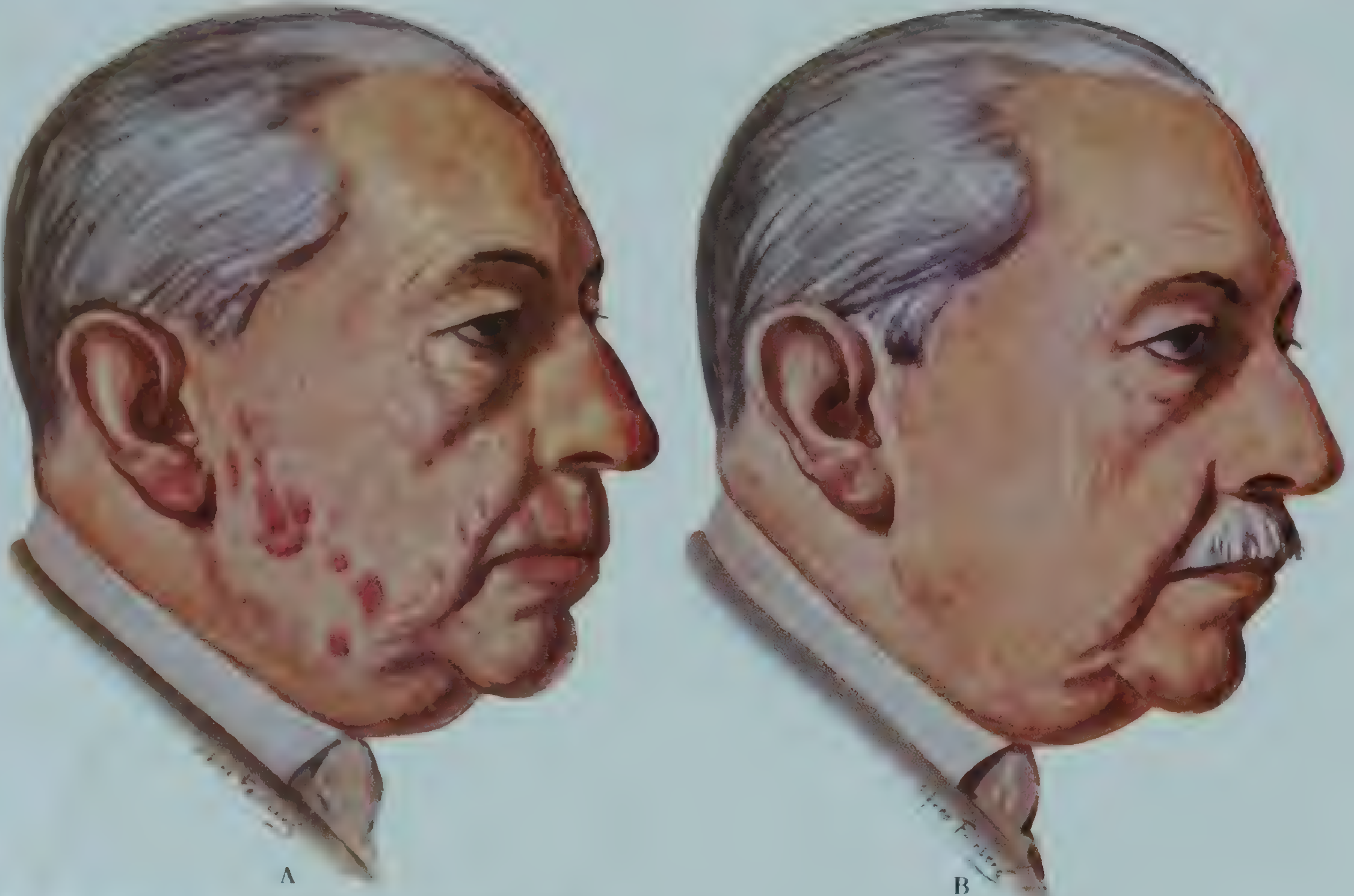

Fig. 28. Case G. G. A, Lupus erythematosus, discoid type, before treatment. B, Lupus erythematosus, discoid type, four months after removal of infected foci.

Comment. No evidence is presented that proves this case as one of allergy, but certainly there are indications of an unusual reactivity to certain bacterial substances of staphylococcus, which was the organism recovered from the ethmoidal tissue. The course of events following removal of infective foci suggests a probable causal relationship between the lupus lesion and the infection, and the blood eosinophilia permits speculation as to a possible allergic basis.

In view of the fact that to the present no other idea has been advanced in explanation of this disease, the hypothesis of bacterial allergy should be given careful consideration.

The Disseminated Type. Although this form of the disease receives its name from the cutaneous lesions evident during its course, it is in reality a systemic, sex limited (female) disease with varied and widespread visceral lesions. It is practically always fatal, after a course of varied intensity and acuity lasting from a few months to a few years. Rose and Pillsbury[37] report a case of twenty-four years' duration.

The cutaneous lesions are polymorphic, usually on the exposed parts, with the typical butterfly lesion over the nose and cheeks as in the chronic discoid type, but lesions can and do occur on any part of the body, and mucous membranes are at times involved. The lesions are described as erythematous, eczematous, bullous, hemorrhagic, ulcerative and edematous (circumscribed or diffuse).

The systemic symptoms during acute phases are those of any acute infection, with fever, malaise, loss of weight, leukocytosis or leukopenia, more often the latter, and general aches and pains. In addition, the clinical picture is varied depending upon the organs that are implicated, for lung, heart, liver, spleen, kidney, serous membranes and bone marrow are all subject to involvement largely as a result of the lesions of the entire vascular system.

The pathology of the disease has been thoroughly presented by Klemperer, Pollack and Baehr[38] and need not be reviewed here.

Etiology. It is noteworthy that with all of the study that has been done, the cause of the disease is as much an enigma as when it was first described some fifty years ago. It is possible to relate this disease with the varied manifestations of the erythema group as developed by Osler[29, 30, 31] and previously referred to. That it is not a tuberculous process is quite generally admitted, nor has it been possible to relate the disease to any specific infection. It is reasonable, however, to consider the possibility and the evidence in favor of tissue sensitization as the basis for the varied lesions of the disease known as lupus erythematosus.

It is today quite definitely established, largely through the work of Rich,[39] that the vascular lesions of periarteritis nodosa have on occasion resulted from a sensitization to the sulfonamides and to horse serum. In other cases the arteritis appears to be the result of a bacterial allergy.

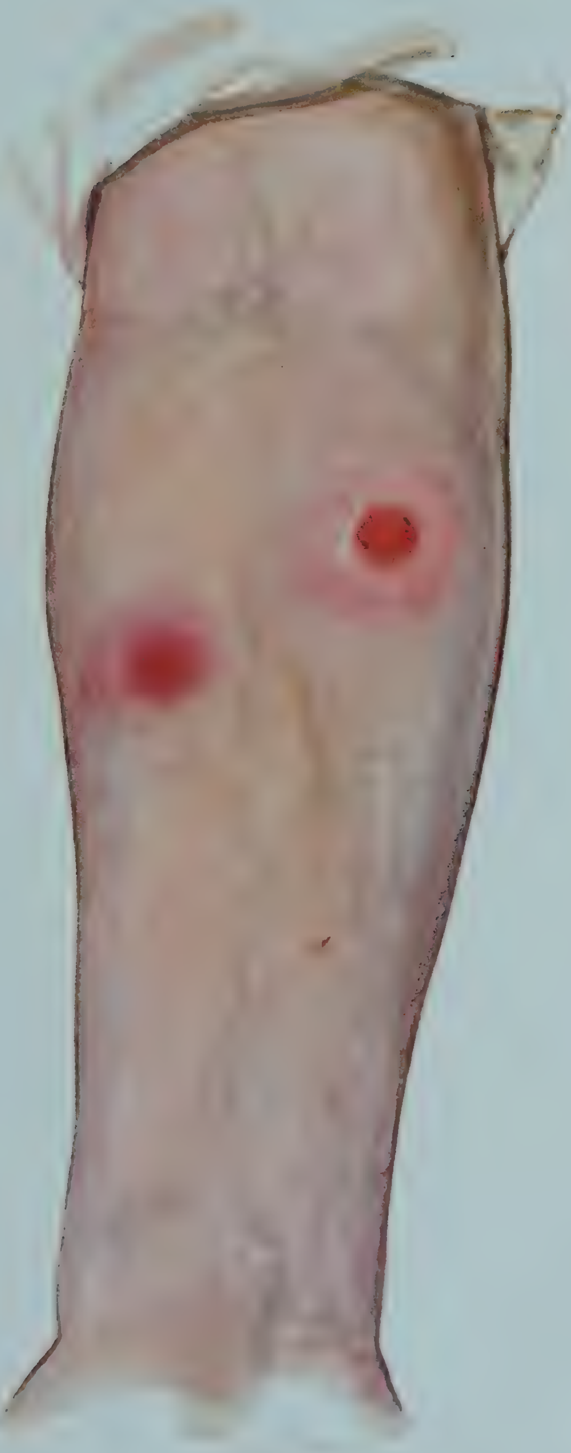

Fig. 29.—Case G. G. The delayed intradermal skin reaction with staphylococcus toxin filtrate 1:100 dilution.

In a large proportion of the recently recorded cases of periarteritis nodosa asthma has been present, usually for years prior to the onset of the vascular disease, and in my own experience the cause of asthma in such cases has been infective, in other words a bacterial allergy. This is not the type of allergy in which one would expect to find the typical familial incidence of allergy nor even a past history of personal allergies. It is, of course, not a valid argument that because periarteritis may be an allergy the vascular lesions of lupus must also be, neither does it negative the concept, for we do not know all the varied possibilities of tissue reaction based on sensitization. More suggestive as positive evidence of the close relationship of these two vascular lesions is the finding by Volk[40] of their coexistence in a case reported by him.

The following brief report of a case in my service at the Roosevelt Hospital illustrates the clinical association of asthma with a systemic disease which terminated fatally, and in which autopsy findings permitted a diagnosis of disseminated lupus.

E. C., a girl aged eight years, was admitted in February 1938 with a history of asthma of five months' duration. She was sent home from school on account of a "bronchial cold," and that night, because of severe dyspnea, she was seen by a physician who made the diagnosis of asthma.

Two weeks later another "cold" was followed by asthma, and so for the balance of five months one cold followed another usually with asthma for several days.

She was a well-nourished child, weighing sixty-four pounds, with typical chest signs of asthma. Skin tests were positive to dog dander, dust and horse serum. The roentgenograms showed evidence of a large adenoid mass and marked thickening of the antral membranes. Under treatment, and after getting rid of the family dog, her asthma failed to improve. An adenoidectomy was done in June 1939 when she was still a healthy, well-nourished child. After four months she returned to the hospital, in October 1939, on account of a loss of twenty-five pounds and malaise, asthma, and abdominal cramps, joint and muscle pains and painful "lumps" on her forehead and scalp which appeared and disappeared. She also complained of burning spots on the palms and fingers.

The child was emaciated, there were râles and sibilant sounds throughout the chest, and a loud systolic heart murmur. The leukocyte count was 31,000, with 51 per cent eosinophils. The erythrocyte count and hemolgobin were normal. Roentgenograms of the chest showed diffuse, patchy areas of consolidation, and those of the sinuses indicated pansinusitis.

A sternal puncture revealed an increase of mature eosinophile cells, and a muscle biopsy did not show any vascular changes. The maximum leukocyte count was 46,500 with 69 per cent eosinophile cells. The urine was at that time normal.

After careful feeding and vitamin therapy there was sufficient general improvement to warrant a bilateral sinus operation which was performed in November 1939 by Dr. Grove. He found extensive polypoid degeneration of the mucous membrane of both antrums. The patient's condition then changed for the better. Within six weeks asthma and abdominal pain were less, the leukocyte count was 15,000 and eosinophils 2.5 per cent. They were never again increased above these figures.

She returned home and continued to gain for about six months. Her asthma practically disappeared, but a new chain of symptoms developed. She had several attacks of severe bloody diarrhea. There was numbness and tingling of the little fingers and an herpetic eruption along the right median nerve. There were swellings of the feet and ankles and the soft tissues of the arms and legs. There were diffuse, burning edemas which became purpuric as swellings disappeared.

Gradually there were evidences of circulatory failure with enlarged liver, fluid in the right side of the chest and in the abdomen. The urine showed albumin, hyaline and granular casts. With occasional periods of improvement the course was progressively downward, and after what was diagnosed as an acute bronchitis she died at home in October 1941.

Consent for autopsy was obtained, and the following is the synopsis of Dr. Brandes' report:

Nephrosclerosis. Infarction of left kidney.
Cor pulmonale.
Passive hyperemia of liver, lungs, stomach and intestine.
General anasarca. Multiple ulcerations of legs, multiple serositis.

Note: "The renal lesions along with serosal and cardiac lesions are suggestive of those found in lupus erythematosus disseminatus."

Comment. This unusual case beginning with asthma in a child with positive immediate wheal reactions, developing a temporary symptomatic eosinophilic leukemia and progressively showing evidences of widespread systemic disease with postmortem findings indicative of disseminated lupus, indicates the probability of a single basic biologic process. The asthmatic feature while primarily of a simple inhalant nature developed into a typical infective asthma. This suggests that the same bacterial allergy was a factor in the general systemic disease.

Treatment. There is, at present, no recognized treatment for this disease which has been uniformly fatal. On the assumption that bacterial allergy might account for a certain number of these cases, the discovery of and attention to areas of focal infection by means of surgery and the adequate use of antibiotics and vaccines might prove of real value. This, however, is with the proviso that possibilities in the case are recognized early and treatment promptly instituted.

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Section V

ALLERGY OF THE NERVOUS SYSTEM

19. *Allergic Neuropathies*

ROBERT A. COOKE

IN NEUROLOGY many symptom complexes that are definite, as well as those that are vague and ill-defined, rest upon an uncertain or unknown pathogenesis and etiology. The concept of allergy has been invoked in an attempt to throw greater light on the origin and cause of such syndromes. The evidence for hypersensitivity as a possible explanation rests upon experimental and clinical studies.

Experimental Neurology

Hashimato[1] observed a significant drop in body temperature of sensitized animals when an intracerebral (corpus striatum) injection of antigen was made. Spiegel and Kubo[2] found that a fall of blood pressure occurred in sensitized dogs if the antigen was injected into the carotid artery. Davidoff and Kopeloff[3] (1931) sensitized dogs intravenously and cerebrally. Antigen (serum) and agar were introduced into one motor area with the idea that a local inflammatory reaction to agar would stimulate greater local sensitivity. The shocking intravenous dose produced transient hemiplegia.

A brain lesion of the Arthus type was produced in the rabbit by Davidoff, Seegal and Seegal[4] (1932). Sensitization was produced by injections into the brain as well as by the intravenous route. The shocking dose produced symptoms referable to lesions of the brain. The immediate systemic reaction was not particularly evident. General and cerebral anaphylaxis was produced in the monkey by Kopeloff, Davidoff and Kopeloff[5] (1936). Large amounts of antigen were required. One significant point is the finding that fatal anaphylaxis and an Arthus-like reaction in the brain were produced without evidence of circulating antibody (precipitin). Alexander and Campbell[6] (1937), using guinea pigs, in general confirmed the production of the Arthus-type lesion following intracerebral injections into sensitized animals.

After general anaphylactic shock in animals, changes in nerve cells were observed by Rachmanow,[7] by Weinberg,[8] by Feuillié and Thiers,[9] and by Stief and Tokay.[10] The last described two types of lesion, one vascular, indicated by hemorrhage, and the other parenchymal and degenerative. Garcin et al.[11] and Baginski et al.[12] have also described scattered brain lesions resulting from anaphylactic shock.

Studying the encephalomyelitis which occurs during antirabic vaccination, Rivers and Schwentker[39] gave intramuscular injections of aqueous and alcohol-ether extracts of sterile normal rabbit brain to monkeys. Six of eight monkeys showed either ataxia or paralysis. Seven showed "pathologic changes accompanied by myelin destruction." The nature and mechanism of production of the lesions were not explainable as due to any culturable or transmissible agent. However, the results followed the technic employed in experimental anaphylaxis.

More recently, Jervis[13] and his associates have studied the neuropathology of experimental anaphylaxis in monkeys. They describe the histology of a typical Arthus lesion occurring at the site of antigen injection in the brain, characterized by necrosis, and of a second type of "circumscribed foci disseminated throughout both the white matter of the hemisphere opposite that containing the local reaction and the white matter of the midbrain, cerebellum, pons and medulla." Among the many cellular elements in these areas were "lymphocytes, plasma cells, polynuclear leucocytes (many of which appeared eosinophilic), and peculiar giant cells containing numerous nuclei." Interestingly enough the blood vessels did not show significant alteration. In a consideration of the pathogenesis of these focal lesions the authors feel that they are not a direct result of a general allergic reaction and are not adequately explained as due to multiple thrombi. Ferraro and Jervis[14] (1940) had previously provoked a disseminated encephalopathy in the monkey by the repeated injection of an emulsion of rabbit brain. The lesion thus produced bore a striking similarity to the morphology of the focal lesions mentioned above; hence the same hypothesis is applicable to both, namely "that the pathologic changes in the brain were due to brain-specific antibodies," the antigen for which is the damaged brain tissue from the Arthus lesion in combination with the foreign protein which produced the Arthus lesion. As they state "Tentatively, the mechanism of the lesion may then be visualized as follows: the intracerebral injection produces some damage in the nerve tissue, as evidenced by the extensive local necrosis. The brain tissue, more particularly the myelin sheaths which presumably contain a specific hapten group, is acted upon by egg white, which as a foreign protein substance is capable of acting as a *Schlepper*. The combination of hapten and *Schlepper* produces a 'complete antigen.' The damaged brain tissue being eventually absorbed by the body, complete antigens enter into the general circulation and thus may produce brain-specific antibodies which will in turn react on the brain tissue, giving rise to the pathologic picture described here." The assumption is that the antigen is a lipoid (hapten) activated by a protein. However, Bailey and Gardner [15, 16] have shown that the anaphylactogen of brain broth used in their experiments was soluble in water and insoluble in ethyl alcohol—in other words, not a lipoid. Their experiments are of interest in that they confirm earlier work[17, 18] showing that brain tissue has immunologic capacity and shows, as does lens protein, organ, not species, specificity. They accomplished sensitization by the intraperitoneal injection into rabbits of a heat-killed vaccine of Pasteurella boviseptica grown on rat-brain broth for thirty-six hours.

This brief review of immunopathologic studies in experimental neurology indicates that (1) lesions occur in the brain as a result of local or general anaphylaxis. (2) Both a water-soluble and an alcohol-soluble (lipoid) constituent of brain tissue have been shown to be antigenic. Brain tissue is organ, not species, specific. (3) Two types of lesion may be produced, one an Arthus-like phenomenon and a second consisting, in the monkey, of disseminated foci throughout the brain and hypothesized as due to brain-specific antibodies.

In view of the fact that in experimental anaphylaxis somatic antibodies for smooth muscle tissue and for skin have been demonstrated (see p. 63), there is no reason why cellular antibodies for brain or other tissue may not be formed under proper conditions. The experimental data clearly show that the ectodermal tissue of the central nervous system, like the skin and mucous membrane, is susceptible to sensitization.

The protean symptomatology of the spontaneous neurologic lesions of man, for which allergy has been offered as an explanation, is not satisfactorily duplicated by the experimental work. However, the histology of the experimental lesions described above may correspond to that of some of the spontaneous lesions of man, giving a better understanding of them since the pathogenesis of the experimental lesions is known.

Clinical Neurology

Pathologic data are lacking in the vast majority of patients in whom a diagnosis of allergy has been made, for they do not die during the first stages of neurologic symptoms when an edema or other histologic evidence of allergy might be observed in its primary form before secondary inflammatory or degenerative changes have developed. A pathologic basis for allergy of the central nervous system in man therefore does not now exist, and one must depend upon analogies and other clinical relationships for an hypothesis of allergy.

The evidence for an assumption of allergy may be based upon (1) the fact that the patient is actually or potentially an allergic person; this information may be gained from the history of allergy in antecedents, siblings, descendants, or in the patient himself, either as past or existing allergies. The story of urticarial or angioedematous attacks concurrent with the neurologic symptoms is frequently recorded and is highly significant, while the history of entirely dissociated allergies is suggestive in indicating the basic constitutional defect. (2) A history of recurring attacks of the same or of a similar clinical nature not properly explained as caused by any known organic or functional disease. For the most part the attacks occur at intervals of varying frequency with, usually, complete restoration of function at least in the early stages. (3) A story of some very unusual contact: the parenteral injection of therapeutic serums or biologicals producing neuritis, as antitetanic serum, or the excessive use of some food (Pardee's[19] chocolate case, p. 330). (4) Skin tests: these are of little value as aids in an etiologic diagnosis for they are usually negative even in cases associated with cutaneous edemas. Like most of the angioedemas, the lesion is produced by a delayed type of allergy that is not susceptible to diagnosis by an immediate wheal reaction. However, if properly performed, when positive and confirmed by retest, at least they indicate the allergic constitution of the patient and may be etiologically significant on occasion.

Pathology. Varying histologic changes are encountered in the allergy of man, any one of which might explain a neurologic symptom complex.

Edema and hyperemia of the urticaria-angioedema type are most commonly thought of to explain the symptoms and signs, largely because a cutaneous lesion of this type has been concurrent in many of the reported cases. That this concept may be correct for intracranial edemas is supported to some extent by the normal findings in the spinal fluid in many recorded cases.

However, there are in allergy such other lesions as hemorrhagic, exudative, productive and necrotizing inflammations as seen in the purpura-erythema group, eczema and periarteritis. It is purely speculative that such neurologic lesions may occur, but they are possible explanations of the reactions in the ectodermal tissue of the nervous system although they have never been described.

Etiology. In cases which have been recorded and in which an allergy appears to have been adequately proven, there are three groups of allergenic substances:

Foods. Especially milk, egg, shellfish and chocolate have been recorded as causative factors. Any food may be a possibility.

Drugs and Biologicals. Serums and antiserums, especially that against tetanus, and all protein-containing substances as liver extract as well as many drugs may be allergens. Only a few of the last are of special and verified significance, namely arsenic, quinine, sulfonamides and nirvanol. In drugs it is difficult to separate toxic from allergic effects.

In this connection should be mentioned a most interesting case due to honey bee sting reported by Ross.[20]

Infections. That sensitization to bacteria or their products is an explanation for many allergic diseases is well established, but neurologic literature as yet yields little information either clinical or experimental. A most suggestive case is one reported by Kennedy[21] of urticaria and polyneuritis following an injection of typhoid vaccine.

That this field warrants further exploration and investigation is indicated by Kennedy[38] in a study of infections implicating the nervous system when he says, "Indeed, one feels that the comparative paucity of infecting foci found in our Bellevue groups of nervous system infections may be due to the absence of the correlation of cause and effect in the minds of the examiners." If this be true in direct infection it is certainly much more so in those neurologic lesions that might be proven to be based upon a sensitization to bacterial products from distant foci that operate indirectly through the medium of allergy. In all infections, however, one must be careful not to confound the effect of bacterial toxins on nerve tissue with that resulting from sensitization.

Symptomatology. The clinical evidences of allergy of the cerebral and peripheral nervous system depend upon the location of the lesion and probably also upon the pathologic and immunologic type of allergy. There are therefore cases with paroxysmal epileptoid attacks, retrobulbar neuritis, and symptoms suggestive of encephalitis or multiple sclerosis. Headache, blindness, deafness, vertigo, ataxia, aphasia, somnolence, coma, paralyses and many other symptoms may arise, depending upon the centers affected by the lesion. I shall consider first the central and then the peripheral nervous system.

Symptoms of Allergy of the Central Nervous System. ENCEPHALOPATHY. Cases have been recorded in which the clinical study and the course of the disease indicate the probability that temporary localized and migrating edemas may cause the symptoms. The association of various other clinical sensitizations favors the idea of an allergic basis for the edema. A case in point is one I saw with Dr. Foster Kennedy several years ago.

A physician, then thirty-eight years old, had a negative antecedent but a positive personal history of allergy. He had pollen hay fever. Banana, mushroom and shad roe produced abdominal pain in two to three hours One day he noticed blurred vision in the right eye. Three days later there was complete scotoma with paresthesia of the right side of the body. The patient has no recollection of the ensuing five weeks, during which time he was in a state of somnolence and semicoma with great restlessness. A right third nerve paralysis and muscle weakness of the right arm and leg developed. Recovery was complete, but three months later there was blindness of the left eye with left-sided paresthesia. From his clinical history and by the use of restrictive diets, beef and pork were proven to produce a return of paresthesia. Fifteen years later, with the patient still on a restricted diet, there has been no return of the central nervous symptoms.

This case is typical in that it occurred in a definitely allergic person and does not fit into the framework of any definite organic disease. Several similar cases are recorded in neurologic literature. Another example among my histories is a case I saw in 1932.

A woman fifty-five years old was hospitalized for a general physical examination. At various times in the past, liver extract had been given subcutaneously for a mild secondary anemia. She was in good general health and with normal blood pressure.

but, as the hemoglobin was a little low, an injection of liver extract was ordered and given. Within a few minutes the patient complained of general itching, the skin showed mild but general urticaria and definite asthmatic dyspnea developed. Shortly thereafter she became disoriented and passed into a stuporous state. At the time I saw her, she was in coma but could be roused a bit. Her reflexes were sluggish, there was no change in the optic disk, the lungs were clear and the heart rapid with a low blood pressure. A spinal tap was not done. The patient never recovered consciousness and died a week later. On account of the typical allergic reaction in skin and bronchi, and the rapid sequence of cerebral symptoms, there was little doubt in our minds that this was a case of cerebral allergy. An autopsy was not permitted.

It is hardly possible to explain this case on the basis of cerebral edema. It seems more probably explained by such parenchymal lesions as those experimentally produced in monkeys by Ferraro and Jervis,[14] or the vascular lesions described by Rich[22] after serum therapy.

EPILEPSY. Attempts have been made to bring epilepsy into the group of allergic diseases. This is because of its supposedly functional basis, the irregular periodic attacks, and the fact that cases of convulsive seizures simulating epilepsy have been recorded.

Such a case has been reported by Pardee[19] in a student nurse aged twenty-one. After eating chocolate candy and ice cream one evening she had a general convulsion and was incontinent the next morning. A secondary convulsion was followed by frontal headache, drowsiness and loss of memory. She was confused and dull for the next ten days. The blood and spinal fluid were normal, and the neurologic examination essentially negative. Past history disclosed that a few years before she had a severe attack of urticaria which she attributed to chocolate. A year later, again after eating chocolate, she had several convulsive seizures with edema of the right cheek and eye. Examinations, including the spinal fluid, were negative. About six months later there was a repetition of the events, first the taking of chocolate ice cream and some hours later a series of convulsions.

Additional cases of convulsions from foods have been collected from the literature by Clark [23] who recorded some cases of his own.

There is little reason to doubt that a certain few cases with convulsive seizures represent an allergic cerebral reaction, but this does not mean that "idiopathic" epilepsy in general is to be regarded as one of the diseases of allergy. Continued study is indicated, especially in those with familial and personal histories of allergy, and certain precautions are in order as follows. There should be a cooperative study by neurologist and allergist and cases should not be regarded as diagnosed unless a symptomatic reaction has been reproduced, as happened unwittingly in the case of Pardee previously cited, or unless the patient under allergic restrictions has been symptom-free for five years while under observation.

MULTIPLE SCLEROSIS. Kennedy[24] has suggested the possibility that this disease of unknown etiology should be studied from the standpoint of allergy. As he states, "its episodes, its intermissions, the curability of its most acute crises, its attack on the optic nerves, its neglect of sensory paths—all these things greatly resemble the happenings of localized allergic edemas," also "the recent plaques in the rare autopsies of acute cases are not sclerotic; they are infiltrations by fluid of the nerve tissue surrounding blood vessels—what the agent may be that makes the coats of these vessels permeable by serum we do not yet know, but the morbid process is suggestively similar to those we have had under consideration." Certain it is that the retrobulbar neuritis which is often an early sign and one on which a diagnosis of multiple sclerosis is often made may be allergic, and may or may not be the early evidence of multiple sclerosis. An interruption of recurring attacks of blindness by the removal of a definite focus of infection in a case authoritatively diagnosed as multiple sclerosis is instanced in the following case referred to me for an allergic study by Dr. Kennedy.

A young English girl, twenty years of age, had been for two years subject to frequent attacks of monocular blindness in the right or left eye. Blindness was partial or complete, at which time the pupils showed the retrobulbar reaction. There was no double vision, no paresthesia, and no sphincter disturbance. The patient had a history of urticaria, eczema in early childhood, and rabbits gave her attacks of asthma, thus indicating her allergic constitution. There were no food sensitivities clinically or by skin test, but rabbit dander gave a positive wheal reaction. The tonsils were grossly infected and a pure culture of Streptococcus viridans was obtained from them. Tonsillectomy was done and an autogenous vaccine used. After six years' observation she had never had a return of the eye symptoms, and no other neurologic disturbance of any kind had developed.

This may never have been multiple sclerosis even in the making, and yet it might have been had not its course been interrupted. Further consideration must be given to Kennedy's[24] suggestion, at least in patients with evidence of the allergic constitution, and the precautions stipulated for the study of epilepsy must be observed.

HEADACHE. The causes of headache are as manifold as the symptom is common. The term is not synonymous with migraine, which as von Storch[25] says is a particular syndrome made up of four cardinal components in the following order of diagnostic importance: (1) recurrent headache, preferably but not necessarily hemicranial, (2) associated visual symptoms, classically scintillating scotomas, (3) temporary gastro-intestinal phenomena, usually nausea or vomiting, and (4) hereditary migraine diathesis, occasionally an epileptic history. See the following chapter on migraine.

As for the simple non-migrainous headache, this may be the result of an allergic response and this possibility was well presented by Eyermann[26] in a study of sixty-three cases. His suggestion of the term "allergic headache" is sound for those cases that are proven to be based on a hypersensitive reaction.

In the diagnosis of allergic headache significant points are (1) a background of sensitization in the family or personal history. This occurs in a large percentage of cases. (2) A positive clinical test. The symptomatic reaction (headache) should be elicited by an appropriate contact with whatever allergen has been found to be the cause. (3) A complete cessation of recurring attacks of long duration through the avoidance of causes when observed for several years.

Cerebral edema or hyperemia is the probable explanation in most cases. Foods and infection have been proven causes. Inhalants are of little importance save as they may produce nasal edema which indirectly is a cause of headache. This therefore is not a true allergic headache.

The one point on which I would differ with Eyermann[26] is in the diagnostic value of skin tests. Rarely in my experience has the food eventually proven to be the cause given an immediate wheal reaction. When it did so, the patient had usually been aware that this food caused headache. One patient under study for asthma failed to state a known allergy to chocolate. Immediately after a skin test with chocolate she said "I smell chocolate. That always gives me a terrific headache." The skin test was markedly positive and the headache began within five minutes and lasted twenty-four hours. This is one of but three such cases I have ever encountered, another being a boy reacting to egg, and the other a woman sensitive to spinach.

For the most part I have found skin tests of little use, as the food-sensitive cases have been examples of "delayed allergy." One good example of this occurred in a well known surgeon in New York City who had headaches for years. On a vacation at one of the French spas he was given the simple European breakfast and the headaches disappeared. On a visit to England and with his usual breakfast, including an egg, the headaches gradually began again. He returned to France and with coffee and roll again for breakfast the headaches vanished. It finally became evident that egg was a cause, for by eating or not eating egg he could produce the headaches or be free of them. This was a delayed reaction, not the prompt type of allergy with an immediate skin reaction.

Another one of my patients always had a headache beginning twenty-four hours after a pollen injection for hay fever. Even the purified pollen protein gave this reaction which was "delayed" and not a part of any immediate constitutional reaction. Although her hay fever was controlled the patient preferred it to the headaches, which were severe.

However, a word of caution must be entered against the too ready acceptance of allergy in explanation of headache. Too many patients are being too rigidly dieted too long and to their detriment when a careful examination would disclose the real cause. I recall a patient with seasonal hay fever and perennial headaches who had lived under excessive restrictions for a year without improvement when the proper diagnosis for the headache was hyperostosis frontalis interna.

SOMNOLENCE. Only a few cases have been recorded as due to allergy.

May[27] reported one (1923). Sternberg[28] had a case which I was privileged to follow. The patient had seasonal somnolence in August and September for eleven years. He had no hay fever but gave a marked wheal reaction to ragweed pollen extract. Under treatment with the pollen injections he carried on his business without the usual six weeks' interruption.

SYNCOPE. A rare type of case that I have not found in the literature is represented by that of a dentist's assistant who consulted me many years ago. Shortly after she started this work she fell suddenly to the floor one day in a complete faint, with mild asthmatic breathing, from which she recovered promptly. After this had occurred several times she became aware that it happened every time and as soon as she opened a bottle of dentalone to hand to the dentist. It was surmised these were attacks of petit mal though she had never had anything like it before. In my office we allowed her to smell in turn the three essential oils in this preparation. Oil of myrrh and oil of bergamot had no effect. With the oil of cassia, syncope immediately occurred. The attack was brief and recovery complete. Were it not for the history of other allergies both personal and familial one could not credit this as an allergy. I have seen one other case of syncope in an asthmatic patient which was caused by amyl acetate.

Symptoms of Allergy of the Peripheral Nervous System. PERIPHERAL NERVE ALLERGY. Since the introduction of therapeutic serums, particularly tetanus antitoxin, neuritis and polyneuritis occasionally associated with symptoms of cerebral and cord lesions have become fairly common as a part of the serum disease, but a few cases following serum therapy without evident serum rash are recorded. The earliest record, according to Pollet,[29] was that of Engelmann in 1897, followed by that of Gardere and Gangolphe[30] in 1908. Since then well over a hundred cases have been reported. Young[31] summarized fifty cases in 1932.

The site of predilection is the cervical plexus, but the lumbar and sciatic nerves have been implicated as well as cranial nerves. Mason[32] reporting on optic neuritis with serum disease in 1922 states that after his first case he made a careful search of the literature and found no other cases recorded. However, an ophthalmoscopic examination of all patients under serum therapy shortly revealed to him two more cases, indicating that this is not a rare condition when looked for.

The definite relation to serum therapy and serum disease stamps this type of neuritis as a part of the allergic reaction. The lesion causing neuritis is presumably a perineural edema of the same nature as urticaria. Motor nerves are more frequently involved. Paralysis is prompt, usually less than a week following the onset of urticaria, but it may be as late as two to three weeks. Most of the cases recover completely over a period of months, but the prognosis according to Young "is determined by the occurrence of atrophy. In those cases in which atrophy is not noted in from six weeks to two months the prognosis is good. In cases in which atrophy occurs the prognosis is poor." There is no known method of prevention of this complication for, like serum disease, it is one of the hazards of serum therapy.

A second and less frequent but highly significant form of neuritis that may be based on allergy is that resulting from the therapeutic use of bacterial vaccines. In Young's[31] collected series, two patients developed neuritis after typhoid vaccine, and one after staphylococcus vaccine. In Kennedy's[21] case following typhoid vaccine there was severe urticaria followed by paralysis.

There is some ground for the belief that infection itself, bacterial or viral and acute or chronic, may produce its effects on nerve tissue by an allergic rather than a toxic action. Another of Kennedy's[24] cases, an allergic individual, following a respiratory infection had migrating palsies which did not clear until after radical sinus surgery. The lesion was diagnosed as one of periradicular edema of fluctuating severity and site.

Foods have also been regarded as causes by Duke,[33] Mathieu,[34] Rowe and Richet,[35] Vaughan and Hawk[36] and others.[37] The cases to date are not too soundly substantiated. Certainly they are not common. However, there is no reason to believe that, in association with other allergies as urticaria and agioedema from food, symptoms of peripheral nerve involvement might not occur as well as similar lesions within the brain.

Diagnosis. One of the typical features of the peripheral and central neuropathies attributed to allergy is the varied, often wandering, type of lesion which has recurrences but no permanency, at least in the early stages. However, severe or prolonged pressure may lead to degeneration of nerves, as in the cases of paralysis of the circumflex nerves after injections of antitetanic serum reported by Kennedy. The frequency with which nerve paralysis has followed this particular antiserum as compared with other serums gives rise to the speculation that this may have a special property of neuron affinity derived from the tetanus toxin that produced it.

To make diagnoses of allergy it is necessary to think in terms of allergy, to be "allergy-minded," but this tendency must be balanced by a determined effort to disprove as well as to prove the thesis and the question should be approached cautiously and conservatively and in association with a neurologist.

For an *assumption* of *allergy* one should bear in mind the six cardinal points previously stated on p. 35. But for *proof* of *allergy* (1) one must obtain a symptomatic reaction following the proper exhibition of the offending allergen elicited at least three times under identical conditions. Such evidence, however, is rarely warranted in practice on account of the hazard involved, though it may be secured from a careful history as instanced by Pardee's[19] case of chocolate sensitivity. This danger is one of the reasons for the slow development of allergy in clinical neurology. (2) Or following a presumed etiologic diagnosis there must be a definite and complete interruption of previous symptoms for five year under observation during management directed against the cause.

In the study of a case assumed to be an allergy the usual procedures include dietetic modifications with avoidance of suspected foods and drugs for periods of two to four weeks at least. A careful search for foci of infection must be made in addition to the general physical and neurologic examination. Skin tests may be done but they must be interpreted with caution. A positive test may have no significance; a negative test does not rule out a possible allergen.

Prognosis. In neuropathies of allergic origin the outlook for the prevention of symptoms and for cure is good if a diagnosis of cause is made early, before frequent recurrences have given rise to a secondary degeneration which may be permanent or may require months to effect a return of function.

Treatment. In so far as the allergy phase is concerned treatment consists merely in avoidance or removal of the cause. Since an allergic constitution is likely to be permanent or at least of long duration the patient must be carefully instructed as to the dangers of recurrences from the same or different types of allergens. For example, after a neuritis due to serum, any such therapy in the future would be hazardous in the extreme.

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20. *Migraine*

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MIGRAINE is a syndrome with a complex pathophysiology in which hereditary influences play an important role. This is apparent in the frequency with which a family history of migraine or allergy and, at times, convulsive states is obtained. According to Scott[1] there is a familial history of periodic headaches in almost 90 per cent of the cases of migraine. Bassoe,[2] investigating a group of 270 patients suffering with this disease, showed evidence of the previous existence of migraine in 57 per cent of the parents, in 8.1 per cent of the grandparents and in 29 per cent of the brothers and sisters. As many as eight individuals in one family have been known to develop some form of the varied manifestations of this syndrome.

According to most workers, migraine is encountered more frequently in women than in men, in a ratio of 3.4 to 1. Allan[3] does not believe that there is any material difference in the incidence of the disease in the two sexes. Flattau[4] points out that this malady is transmitted in 79 per cent of cases through the maternal and in 21 per cent of instances through the paternal line.

The time of life during which migraine makes its first appearance varies. Fifty per cent of patients develop the disease between the ages of twenty and thirty, and the greatest number between the years of sixteen and twenty-five. The onset of migraine in O'Sullivan's[5] group of patients occurred before the age of thirty. It has, however, been frequently encountered in children even as young as two years of age. Some investigators believe that the symptoms may develop for the first time during middle life. While this may be true in some instances one should always be careful to exclude an organic basis for the migraine. In quite a few patients menstruation seems to play a significant role in the initiation of the migraine attacks which may appear either shortly before the menses, coincidentally, or alternately with them. During pregnancy or following normal or induced menopause they may completely disappear. Yet there are patients in whom the cerebral manifestations may become worse during the menopause. The migraine seizures may recur daily, every two or three days, once a week or month, or once each year or two. In most instances no distinct regularity has been noted except in relation to menses. There are occasional cases in which the attacks may be so frequent as to suggest a "status hemicranicus" similar to a status asthmaticus.

Etiology

Among the many factors which have been described as causes of migraine the role of *allergy* is regarded as important. Also of significance are various *endocrine* disturbances, and a *neuropathic* personality. In addition, there are various conditions which have been regarded by some investigators as being fundamental, though in reality they are only precipitating or secondary causes. These include eyestrain, nasal disorders, chorea, rheumatism, visceroptosis, tuberculosis, gout and diabetes. Of more immediate concern is the presence of hypoglycemia (Girard and Colleson[6]), alcoholism, unexpected emotional stimulation, or psychic trauma from various sources.

Allergy. Pagniez, Vallery-Radot and Nast[7] in 1919 were among the first to suggest the implication of an allergic mechanism in migraine. Miller and Raulston,[8] Vaughan,[9] Rowe,[10] Eyermann,[11] Balyeat and Brittain,[12] Rinkel,[13] and others followed. In 1935 Vaughan[14] published statistics to the effect that in 70 per cent of cases, especially if a personal or family history of allergy was obtained, hypersensitiveness proved to be responsible for the migraine headache. In 50 per cent of the patients a reasonable amount of relief was afforded by the exclusion of offending foods determined by the usual methods of investigation, such as skin tests and elimination diets. There is a question in the minds of most investigators whether the high percentage of favorable results reported by Vaughan is not due to the inclusion in his series of cases which fall into the category of "allergic headaches" rather than classical migraine. In interpreting the skin tests Vaughan laid a great deal of stress on borderline as well as delayed reactions. According to this author, for every 100 positive or borderline reactions to foods, an average of fifty were found to be clinically significant. Trial diets and keeping of a food diary were also of great aid in the study of these cases.

In their investigations of migraine, Balyeat and Brittain[12] described a family incidence of allergy in 85.4 per cent of their patients. In O'Sullivan's[15] cases, 90 per cent of those who reacted to various skin tests had a history of hives at some time in the past. Seventy per cent of her patients with migraine were found to be sensitive to various allergens. Eosinophilia of from 3 to 20 per cent has been recorded in one third of the cases, especially in the presence of other allergic conditions. In 50 per cent of the children, however, there is usually a relative lymphocytosis.

In addition to the role of foods and inhalants, the periodic development of migraine in certain cases suggested to some observers that sensitization to a product elaborated in conjunction with menstruation may be responsible for the attacks. In a group of female patients who manifested premenstrual headaches and premenstrual tension associated with symptoms of endocrine dysfunction, Phillips[16] found sharp reactions to intradermally injected synapoidin (a combination of gonadotropin and pituitary extract), whereas control normal subjects gave a negative response. The patients who showed these positive reactions were successfully desensitized by him with the hormonal preparation in question. Working along the same lines Moffat[17] also reported favorable results in similar patients following the injection of the gonadotropic factor of pregnancy urine. Whether the interpretation given by Phillips and Moffat of an allergic mechanism responsible for the migraine attacks is the proper one, or whether the improvement which followed the injection of the hormone products was due to a correction of some endocrine imbalance, as is maintained by the proponents of the endocrine dysfunction hypothesis of migraine, awaits further elucidation.

Endocrine Factors. The advocates of the endocrine dysfunction theory in the causation of migraine have postulated that the basis for premenstrual migraine may be found in a disturbance of estrogen and possibly gonadotropin secretion and excretion during the premenstrual phase. Riley, Brickner and Kurzrok[18] studied eleven female and two male migraine patients and found that during twenty of twenty-nine headaches in the female patients gonadotropins were present before an attack, whereas urinary estrogens were reduced or absent. They also observed that in two males, gonadotropic substance was regularly present in one before each paroxysm, and in the other, in four out of eight attacks. The arguments of these workers in favor of an endocrine factor in the development of migraine are based on the following facts: that migraine frequently appears at puberty before menstruation when estrogen excretion is reduced and gonadotropin appears in the urine, that relief from attacks occurs during pregnancy in some cases at a period of increased estrogen excretion and diminished excretion of pituitary gonadotropic factor, that cessation of attacks follows the conclusion of the menopause, and in the instances of men there is progressive diminution or disappearance of migraine after the fifth and sixth decades. That endocrine substance could have an actually inciting role was suggested by the production of slight but typical attacks after the injection of follutein in seven out of nine patients. Additional evidence cited is the occurence of various endocrine stigmata in migrainous patients. These may consist in the finding of eunuchoidal proportions, Lorain-Levy pituitary type of disturbance accompanied by low metabolic rates, the presence of relative lymphocytosis, increase in uric acid, low normal fasting blood sugar, low urinary output, salt and water retention, as well as scanty menstruation and sterility.

Neurogenic and Psychogenic Factors. Aside from the anatomic and physiologic constitutional abnormalities, the psychogenic pattern of the migrainous patient has been frequently analyzed by numerous investigators. Most observers have noted certain peculiar characteristics in the make-up of the person subject to migraine. These are strong self-criticism, blocking of emotional expression, meticulosity, perfectionism and the like. Slight and Morrison[19] refer to the existence of an "imbalance of the effector system for free and external expression." In most of these patients there seems to be an antagonism between the patient's native inhibitions and the desire for expression in keeping with the degree of excitability and consequent tension that he is capable of developing. Selinsky,[20] who analyzed 200 patients with migraine, considers that the headache is an escape from a world of too much activity into inactivity induced by headache, "the fearful helplessness and frantic effort to reject something insufferable to the ego." Some of the women patients resented being female and suffered considerably at menstrual periods.

Mechanisms of Migraine

According to most observers the polymorphous manifestations of migraine are the results of abnormal reactions in the blood vessels in different areas of the brain in response to various stimuli of allergenic and non-allergenic origin. Rodella[21] describes the vascular reactions during an attack as consisting of three phases:

(1) Vascular spasm in the region of the large and medium-sized arteries and veins, especially vertebral vessels.

(2) Vascular dilatation due to liberation of vasodilating substances in the ischemic region of the brain.

(3) Formation of an exudate in the pia.

During the stage of vascular dilatation Rodella found widening of the retinal vessels. Critchley[22] also noted engorgement and tenderness of the temporal vessels with changes in the conjunctival and retinal vessels. The observations of Goltman[23] of the case of a young woman, twenty-six years of age, with typical migraine attacks since childhood, who was subjected to operative intervention because of a suspicion of a brain tumor, offer further support to the concept of vascular involvement in the development of this syndrome. At the time of the operation the patient was having a headache. On exposure, the dura in the left frontal region was tight and non-pulsating, but the blood vessels appeared dilated. When the dura was opened a fair amount of fluid escaped under increased pressure. The brain looked wet, but there was no tumor. The lateral ventricle was opened and here too there was an increased quantity of cerebrospinal fluid. Air injected into the ventricle excluded the existence of a neoplasm. The postoperative diagnosis was edema of of the brain and idiopathic migraine.

Following the exploratory operation she was observed by Goltman during various migrainous attacks. He found that she was sensitive to a number of foods and invariably developed an attack following the ingestion of wheat. The attacks were characterized by (1) vasomotor spasm, as evidenced by blanching of the face and persistence of the depression in the scalp at the area of the trephine opening; (2) secondary vascular dilatation with resulting edema of the brain, manifested by bulging at this site, due to increased cerebrospinal fluid pressure. He believes that the aura, numbness, tingling and eye symptoms may be due to vascular spasm with subsequent temporary ischemia of the brain or part of the brain.

Supplementing these observations are the recently reported findings of Redish and Pelzer[24] on the variations in structure and behavior of the capillaries in patients with migraine. In contrast to the normal they found in the majority of their patients marked tortuosity, increase in the number of crossings and the occurrence of knottings in the different capillary limbs. In 80 per cent of their patients alterations in the diameter of the capillaries were also present. Microscopic examination of the capillary vessels of the skin and the mucous membrane of the mouth, during migraine attacks, disclosed a blurring of their walls, which became more marked in the presence of nausea. In the headache-free interval such blurring was either absent or diminished in three fourths of the cases. Following the intravenous administration of 0.25 to 0.5 mg. of ergotamine tartrate for the control of the headache, the capillary wall became much clearer and narrower, and the patients experienced subjective relief. After thirty to forty minutes, however, it became blurred again suggesting a disturbance in fluid exchange. To test this hypothesis 1500 ml. of water were administered to fifteen migraine patients. Fourteen of the fifteen patients developed migraine accompanied by blurring of the capillary walls within the period of water retention following the four-hour period of excess excretion. Prompt diuresis in two of the patients following injection of ergotamine tartrate brought about a cessation of headache and a restoration of the capillary outlines. The conclusion drawn by the authors from these experiments is that a relationship exists between the water balance of the body, the state of the capillaries and the migraine seizures. Loss in capillary visibility during attacks is to be attributed to increased transudation of various substances through their walls.

The possibility that similar disturbances occur in the cerebral vessels, and account for the local edema which is responsible for the symptoms of migraine, presents itself for consideration. The concept of Graham and Wolff[25] that an increased amplitude of pulsation of the branches of the external carotid artery is responsible for the headache, inasmuch as reduction of the pulsation relieves the symptoms, is not inconsistent, according to Redish and Pelzer, with the theory that local edema may be the determining factor. They infer that the increased pulsation favors arteriolar dilatation which in turn enhances the passage of fluid through the capillary walls, thus bringing about edema. Schumacher and Wolff[26] believe that the actual pain experienced in migraine is due to stretching and dilatation of the arteries of the scalp and dura, while the prodromal symptoms including the scotomata are the result of occlusive vasoconstriction of the cerebral vessels. Thus they regard the essential migraine phenomena as the result of dysfunction in vascular mechanisms and vascular beds.

Symptomatology

In view of the fact that migraine apparently consists of a vascular response to various stimuli, the character and distribution of the symptoms will depend upon the number of vessels participating in this reaction, and the area of the brain implicated. The symptoms of classical migraine are distinguished from those of ordinary headaches by four cardinal features: (1) prodromal visual phenomena; (2) hemicranial location of the headache; (3) gastro-intestinal manifestations; and (4) vasomotor phenomena.

Prodromal Manifestations. While in some instances there may be no warning signs of the impending attack, the majority of patients may experience for some hours or days prior to the onset of the migrainous seizure a sense of general malaise and a feeling of helplessness. Some persons may feel a heaviness in the head or eyelids, and easy fatigability; others may be irritable, restless or somnolent. There are those who may be euphoric, abnormally hungry, or may complain of gastro-intestinal disturbances such as nausea, diarrhea and transient abdominal pains.

The actual attack is preceded by certain aura consisting as a rule of variegated visual phenomena. These may be characterized by scintillating scotoma, blurred vision, photophobia, the visualization of colored spots of different sizes and configuration. There also may be areas of visual impairment ranging all the way from scotoma through hemianopsia to occasional complete blindness. Certain patients have described the sudden advent of zigzag lights, so-called "fortification spectra," as well as silver bugs in continuous motion. Others, according to Riley,[27] have reported oscillatory, shimmering or vibrating distortion in the appearance of objects whose outline and clarity become blurred, which they liken to a rippling effect on the surface of water. Spinning, darting or irregular bands of light or shimmering points passing rapidly through the visual field have also been recorded. Transitory amblyopia commencing like a light cloud and increasing in extent to complete amaurosis accompanied by black spots is not infrequent. In addition to these visual disturbances, hallucinations of smell and taste have been complained of by some patients. The visual phenomena usually last twelve to fifteen minutes and are succeeded by the headache. Occasionally the headache may develop concurrently with the visual phenomena and at times the atter may be the only manifestation of migraine, the headache being temporarily in abeyance. In some subjects it may never even appear.

Migraine Attack. The migrainous seizure may occur at any time of the day or night and even awaken the patient, who may complain of having had some terrifying dream. The headache is most often described as embracing the half of the head, including one eye and spreading over the temple and on to the occipital region. It may remain localized to the front, back, or side of the head or become generalized. Usually it becomes progressively severe until it reaches a point where some patients experience a bursting sensation all over the head. The headache has been referred to as throbbing in character. It has also been compared to the pressure of an iron ring about the head, the strokes of a hammer or the boring of a sharp instrument. It may be accompanied by hyperesthesia of the scalp which may spread down the neck and the shoulders. The pain may alternate from one side of the head to the other and occasionally be bilateral. As the headache increases in intensity, nausea and paroxysmal vomiting supervene. The latter may be associated with retching and ejection of bile-stained material. With the termination of the vomiting the headache may subside gradually or come to a sudden end, but often relief by vomiting is only transient. Yet some patients are so glad to get even this short respite that they try to induce vomiting as much as possible

Vasomotor Symptoms. In association with the headache a variety of vasomotor phenomena may develop which have been attributed either to angiospasm or increased vascular permeability. The angiospastic manifestations consist of pallor, widening of the pupils, contraction of the temporal arteries, salivation and general chilliness. Symptoms which have been designated as angioparalytic, characterized by flushing, constriction of the pupil and generalized sweating, may likewise follow. All of these may be transitory.

Increased vascular permeability is occasionally expressed by the development of angioneurotic edema in various portions of the body, and by urticaria and dermographia. In the gastro-intestinal tract it may take the form of diarrhea and constipation; in the heart it may be signalized by the development of tachycardia or precordial distress simulating angina; in the respiratory tract by symptoms varying from shortness of breath to asthma; in the genito-urinary tract it may be exhibited by albuminuria, urgency and frequency of urination with discharge of pale urine of low specificity gravity. Many of these symptoms are suggestive of an allergic mechanism.

Motor Symptoms. Localized twitching, myoclonic contractions affecting the face, occasionally the arms and hands as well as the legs, indicative of irritation of the motor area may occur. Transient areas of paralysis of the limb on one side, affecting more frequently the upper extremity than the lower, may also accompany the attack. These motor disturbances may shift from one extremity to the other or involve both extremities simultaneously. The appearance of aphasia or agraphia in association with the hemiplegia suggests the participation of the cortex in the vascular response. The development of vertigo, tinnitus, with temporary impairment of hearing, as well as visual disturbances, during the prodromal period are likewise indicative of cortical involvement.

Sensory Disturbances. Disturbance in sensation such as hypesthesia alternating with hyperesthesia, which can be so widespread as to affect one-half or even the entire body, have been observed in some cases. As a rule, these are limited to the finger tips, lips or tongue. Tingling and numbness of varying degree may be accompanied by an actual reduction in the apperception of external stimuli, and not infrequently by true weakness in the affected limb. Such sensory alterations may develop in both upper extremities or pass from one to the other, or affect both limbs on one side. Just as in the instance of the motor disturbances, these sensory aberrations frequently appear on the side opposite to the headache, suggesting their cortical origin. Sensory abnormalities of visual or auditory type may also develop in certain cases. There is an almost universal aversion to light and usually to noise during attacks.

Cerebellar Manifestations. The involvement of the cerebellum may be characterized by disturbances in equilibrium, swaying and dizziness which at times can be sufficiently severe as to interfere with locomotion. Cerebellar asynergia manifested by incoordination and interference in the production of succession movements may under exceptional circumstances also accompany the headache.

Psychic Aberrations. Slowing of mental activity, impairment of memory, incoherence, feeling of anxiety, confusion, insecurity and unrest have been noted in the course of migraine paroxysms and found to continue for some days thereafter.

Postmigrainous Phase. The postmigrainous manifestations which follow an attack vary in duration and character. The return to the normal state is very rapid in most instances. In many it may be as short as fifteen minutes or be prolonged for as long as ten days. Some patients are well after a restful sleep, others are depressed, exhausted and generally "sore" as if someone had beaten them. The nature of the reaction follows a more or less consistent pattern in each individual case. In place of returning to the normal state, migraine may be followed in some instances by permanent derangement in function in tissues which react most markedly during the paroxysm. Depending upon the individual case the involvement may appear in the visual, motor or sensory organs, the vegetative nervous system, or the psychic sphere. Such permanent changes are likely to occur if migraine has persisted for a long time, and have been attributed to permanent alterations in the blood vessels at the sites of previously reversible reactions.

Complications such as hemorrhagic meningitis, thrombosis of retinal vessels and hemorrhage followed by detachment of the retina have also been reported. Dunning[28] described one case and cites five others, in which cerebral hemorrhage occurred during attacks. Five of the patients were women between eighteen and thirty-seven years of age during their first accident. There were ten hemorrhages and one retinal infarction. Only one of the patients died. Three cerebral hemorrhages occurred during menstruation, five (three ocular and two cerebral) appeared at the time of the headache, and were precipitated by activity causing sudden increase in pressure within the blood vessels of the head. In none of these cases was hypertension or cerebral arteriosclerosis demonstrable.

The ultimate disappearance of attacks of migraine has been attributed by various authors to the development of arteriosclerosis in the reacting vessels thus depriving them permanently of their contractile junction, and hence precluding a favorable prognosis. This, however, need not be so, for in some cases disappearance of migrainous attacks may be followed by the development of symptoms in some other shock tissue, such as the gastro-intestinal tract for example, commonly observed in allergic states. This shift in the shock organ may possibly be attributed to spontaneous local tissue desensitization.

Classification of Migraine

As a result of the predominance of certain symptoms which depend essentially on the localization of the vascular response, some investigators have divided the migraine syndrome into the following types.

(1) Ophthalmic migraine, in which visual symptoms are most important and may appear before, during or after the headache. These can affect one eye or the entire visual field, producing temporary blindness. In the majority of instances there are no sequelae. In some cases, however, the scotomata or hemianopsia which may follow can persist for several weeks. In severe cases they may become permanent. When this occurs, an underlying organic disease must be ruled out. In 7.2 per cent of cases of ophthalmic migraine distinctive paroxysmal convulsive disorders may appear. These are characterized by petit mal attacks, twilight states or typical convulsive seizures. At times the migrainous seizures may replace epilepsy or vice versa.

(2) Ophthalmoplegic Migraine. This has been described "as a periodic recurrent paralysis of the eye muscles, associated with headache and vomiting." It may occur in the course of a long-established simple migraine. It has been noted in individuals as young as three and as old as seventy years of age. According to Moebius[29] the headache in ophthal-

moplegic migraine is usually situated deeply behind the eye itself or just over the eye. It may be limited to the side of the ophthalmoplegia or occasionally it may be bilateral. Nausea, vomiting and dizziness are not infrequently present. The duration of the paralysis may be two days to one or two weeks, and even several months, with complete return of function. Both the paralysis and the headache may subside simultaneously. Wolff[30] explains the paralysis on the basis of a temporary dilatation or aneurysmal defect of the posterior cerebral artery causing pressure on the oculomotor nerve. In some cases involvement of the third, fourth and sixth cranial nerves has been described. Under such circumstances the external ophthalmoplegia is complete. Occasionally the ophthalmoplegia may be bilateral. In about half the cases reported, partial or complete residual paralytic manifestations may be demonstrable. At necropsy, lesions affecting the oculomotor nerves or the vicinity of the brain stem from which the nerve arises have been found.

(3) *Facioplegic Migraine.* This is characterized by repeated attack of facial palsy in conjunction with the migraine. Whether the association of these manifestations should be regarded as symptomatic of true migraine is doubtful.

(4) *Abdominal Migraine.* Severe abdominal pain together with nausea, vomiting and diarrhea without any apparent organic disease, when accompanied by typical migraine, has been referred to as abdominal migraine. This condition was observed in 30.8 per cent of 169 cases studied by Slight and Morrison. The pain in abdominal migraine is located in the epigastrium. It has been described as paroxysmal, severe, boring or cutting in character and bears no relation to the ingestion of food. In some cases it may be associated with tachycardia. Larval forms in which only nausea, vomiting, or perhaps diarrhea may develop without any abdominal pain, or the appearance of symptoms simulating gallbladder disease has also been recorded. The abdominal attacks may also occur independently of migraine, or temporarily disappear with the advent of cerebral symptoms and in some cases entirely replace the migrainous seizures.

(5) *Migraine Equivalents.* Typical migraine seizures may be supplanted by or alternate with convulsive attacks, spells of paroxysmal tachycardia or periods of transient mental disorder. Manifestations similar to twilight states in which the patient may be confused and disoriented as to time and place may supervene. Transient manias, periodic episodes of depression and irritability have also been recorded. These have been seen to appear in between the paroxysmal attacks of migraine in 26 per cent of cases. Emotional outbursts, such as anger or weeping, may dissolve a threatened attack of migraine. The migraine may also disappear and symptoms such as neurodermatitis, asthma or vasomotor rhinitis may prevail, only to return when these subside.

Migraine in Children

The migraine headache in children differs in some respects from that seen in adults. The earliest age of onset has been seen in a child of two weeks in whom attacks appeared bi-weekly till the age of seven when they became ophthalmoplegic in character. The prodromal symptoms are characterized by a sense of fatigue, loss of appetite, abdominal discomfort and constipation. The aura are frequently visual. The attack itself is sometimes marked by high fever and occasionally by a lapse of consciousness. The headache when present may be either generalized or unilateral. Nausea and vomiting, as well as abdominal pain, may predominate. The latter may simulate acute appendicitis or acute gall-bladder attacks for which some patients have been operated upon. The vomiting may be so severe as to lead to ketosis. Following the attack, a state of exhaustion and a generalized body soreness may set in. Some children become sleepy, others irritable, delirious and resort to screaming. There may also be polyuria and a nasal discharge of mucus.

According to Bray[31] cyclic vomiting in children may represent the onset of migraine in which nausea and vomiting dominate the clinical picture, whereas the headache and ophthalmic signs are absent. The difference, however, between this type of case and true "cyclic vomiters" is that the latter have negative family histories of allergy and do not give positive skin reactions or have other characteristic allergic stigmata.

Diagnosis

The diagnosis of migraine is justified in cases in which the headache is paroxysmal, associated with evidence of cortical irritation of visual, vasomotor or motor character, as well as with gastro-intestinal symptoms.

Eyermann makes a distinction between this syndrome and the so-called *allergic headache*. The latter is not paroxysmal in character nor is it accompanied by any signs of cortical disturbance. It is, however, frequently associated with allergic reactions in the nose and sinuses, such as may be seen in severe seasonal allergic rhinitis and/or food allergy, and is as a rule brought about by the ingestion of foods. The headache may appear shortly after the offending food has been eaten, or six to twenty-four hours later. It is never severe enough to awaken the patient, and as a matter of fact in some cases may disappear after sleep. It is usually located in the frontal region but at times it may begin over the right or left eye or in the occipital region. Regardless of its original location it has a tendency to spread over the entire head rather than to be limited to one side. The headache has been referred to as being an "ache, a pain, or a fullness as well as throbbing in character." Its duration varies with the amount of incriminating food ingested. Nasal blocking, coryza, dizziness, nausea and vomiting are not infrequently observed. Eyermann found that in patients whose symptoms could be reproduced by feeding of specific foods, the headache was less severe than in the group in which the reacting foods had no influence. In the latter the headaches were most intense, incapacitating and associated with scotoma characteristic of migraine.

A comparison between allergic headache and classical migraine seems to indicate that the difference between the two lies in the degree and localization of the cerebral response rather than in the underlying mechanism. In both instances vascular reactions which bring about spasm and edema in various areas of the brain have been regarded as responsible for the presenting symptoms. Whereas specific hypersensitiveness plays the essential role in allergic headache, in the evolution of migraine not only allergy but endocrine, psychogenic, and other predisposing factors are at play. Just as in cases with allergic headache, patients with typical migraine on an allergic basis who yield positive skin reactions to foods or other substances (approximately 50 per cent, Vaughan), can be more readily controlled than those with negative skin reactions, or those whose symptoms are influenced by endocrine or psychogenic factors, or other less obvious causes.

Histamine Cephalalgia. True migraine must also be distinguished from "histamine cephalalgia" described by Horton.[32] Although the similarity of the latter to migraine lies in its sudden onset and termination, it differs from it in many ways. (See Table 29.) Histamine cephalalgia first appears in the later decades of life. It occurs more often in males than in females. There is usually no family or personal history of allergy, and the skin tests are negative except in those patients in whom both migraine and histamine cephalalgia may co-exist. One such case has come under our observation. There are no prodromal symptoms in histamine cephalalgia such as seen in migraine. As a rule the headache in the typical case begins at night after the patient is asleep. It is associated with profuse watering and congestion of the eyes and severe pain which is continuous and may involve the temple, neck and face. There is rhinorrhea and increase in temperature on the involved side of the head as well as swelling of the temporal vessels. These symptoms are of short duration and last about an hour. They may be relieved by sitting or standing. In thirty-five of seventy-two patients studied by Horton subcutaneous injection of 0.1 to 0.2 mg. of histamine induced typical attacks. Successful treatment of this form of headache may be carried out by the subcutaneous administration of histamine diphosphate. For this purpose 1 ml. ampoules of histamine diphosphate containing 0.1 mg. of histamine base may be used. The initial recommended dose is 0.25 ml. of this solution. This is increased by 0.05 ml. from the first to the sixteenth injection and then remains at 1 ml. until the twentieth and subsequent doses. According to Horton, two injections a day for ten days to three weeks may be necessary. Untoward subjective or objective symptoms such as flushing should be controlled by a 50 per cent reduction of the ensuing dose. Subsequent dosage should be increased if possible. To continue the improvement in some cases a maintenance dose of 1 ml. one to three times a week may be required.

TABLE 29

Differential Diagnosis of Migraine and Histamine Cephalalgia

Factors	*Migraine*	*Histamine Cephalalgia*
Hereditary background	Present	Absent
History of allergy	Present in approximately 50 per cent of cases	Absent
Age of onset	As early as two years of age	Late in life
Premonitory signs	Visual symptoms, blurring, photophobia, scotoma, etc.	None
Headache	Unilateral, especially at the beginning, later may be bilateral	Usually bilateral, generalized, worse in frontal and temporal region, associated with watering or congestion of eye and nose, and rise of temperature on the involved side of the head
Distribution of pain	Mostly in the occipital and suboccipital regions; although deep, feels superficial	
Duration	From few minutes to several days	Less than one hour
Termination	Sudden or gradual	Sudden
Gastro-intestinal symptoms	Nausea and vomiting	None
Treatment	Depends on the underlying cause. Acute attacks relieved by ergotamine	Subcutaneous injection of histamine diphosphate in graduated doses

Headaches other than histamine cephalalgia are not benefited by this form of therapy. Of sixty-three patients with typical histamine headache studied by Horton, forty-eight obtained partial or complete relief for varying periods of time. Of this group thirty were perfectly well, and in eighteen the attacks were decreased in severity as well as frequency.

Treatment

The therapy of typical migraine depends on the careful analysis of the underlying pathogenetic factors. Employing this approach O'Sullivan was able to classify a series of 300 cases into several therapeutic groups based on the manner of the development of their symptoms and the results of treatment. She observed that women whose headaches were specifically related to the menstrual period, particularly those with a history of scanty or delayed menstruation, were relieved by a placental estrogenic extract (emmenin). This was given in the dosage of 2 drams a day and increased to 4 drams a day before the menstrual period. Such treatment was of special value in the small-boned, underweight Lorain-Levy pituitary type of migraine patient. Patients whose headaches occurred in association with menopausal symptoms, or those who had had an ovariectomy preceding the onset of symptoms, or whose body build or menstrual history was suggestive of ovarian hypofunction were relieved by estrogen in oil (progynon B). Of 124 women thus treated seventy-six were improved. Patients whose symptoms were related to fatigue and strain and preceded by intense exhaustion, especially those with basal metabolic rates of minus 20 to minus 30, were relieved by thyroid medication. Thyroid in conjunction with placental estrogen (emmenin) was found to be effective in patients who suffered from severe dysmenorrhea and oligomenorrhea with their migraine.

The pituitary type of patients "with large bones, thick noses, and grimy skins" were relieved by the administration of pituitary extracts. These patients frequently also suffered with menstrual disturbances as well as allergic manifestations.

Treatment of the acute attack of migraine is accomplished most effectively by the administration of *ergotamine tartrate*. Injected subcutaneously in adequate doses it has been found to give relief in 90 per cent of the cases. It is not a cure for migraine and may not be used as a prophylactic measure because of the danger of toxic as well as allergic manifestations which may follow its use. I have observed two instances of ergotamine hypersensitiveness followed by spasm and the obliteration of the pulses of the lower extremities. The subcutaneous administration of ergotamine consists of a trial dose of 0.25 mg. If it proves to be effective in terminating the paroxysm within two hours it may be given during future attacks. This may be repeated if after two or three hours the headache persists, or if it returns within eight to twelve hours. If a patient presents this type of reaction the dosage in future attacks should be increased to 0.5 mg. Such a dose is usually a safe amount and controls the majority of severe attacks. The oral dose advised by von Storch[33] is from 1 to 5 mg. followed by 1 to 2 mg. each hour until a total of 10 to 12 mg. is given. O'Sullivan advocates the use of five 1 mg. tablets, and advises against its repetition within twelve to twenty-four hours. Mouth administration is useless once nausea or vomiting has set in. Contraindications to the use of ergotamine are coronary or peripheral obliterative vascular disease, acute infections, hepatic disease, hypovitaminosis, especially vitamin C deficiency, and pregnancy.

Untoward effects from the use of ergotamine may consist in nausea, vomiting, stiffness of the joints, a sense of constriction in the throat, heaviness of the chest, burning and tingling of the fingers and toes. Many of these symptoms can be counteracted by the administration of 1/100 grain of atropine.

Ergotamine will not relieve headaches other than migraine. Its exact mode of action is unknown. Wolff's[34] observation that ergotamine in therapeutic doses in man constricts the branches of the external carotid arteries, but does not necessarily alter the internal carotid branches, suggests that the action of ergotamine consists in bringing about active constriction of the dorsal and temporal arteries as a result of which migraine is relieved. This would imply according to von Storch that "the common mechanism of migraine headache consists of overstimulation of the dorsal, possibly extracranial, periarterial plexuses through the medium of hypotonic dilatation of the vessels in question."

The nature of the stimuli responsible for the vasodilation, just as in the cases of Ménière's syndrome, must therefore be investigated from the point of view of allergy, disturbed metabolism and neuro-hormonal regulations. In individuals in whom specific emotional upsets tend to induce attacks, psychotherapy may be of value. Improvement in such instances need not necessarily imply psychogenicity, but can mean psycho-precipitation.

Summary

Migraine is a syndrome with a complex pathophysiology in which hereditary influences play an important role.

The exciting causes may be found in allergy to various foods, drugs and inhalants, in endocrine disturbances, and a miscellaneous series of predisposing conditions of neurogenic and psychogenic origin, such as eye strain, and so on.

The mechanism involved consists of abnormal reactions in the vessels in different areas of the brain, characterized by vasospasm and/or increased vascular permeability brought about by allergenic and nonallergenic stimulation.

The cardinal symptoms of migraine consist of (1) prodromal visual phenomena, (2) hemicranial location of the headache, (3) gastrointestinal manifestations such as nausea, vomiting, abdominal discomfort, as well as vasomotor phenomena.

Treatment is based on the establishment of the underlying cause, if that be possible. If allergy plays an important role in a given case, and certainly this is not common, the usual methods of investigation such as skin tests and elimination diets may be undertaken. Endocrine imbalance, metabolic disturbances or psychogenic factors must be corrected by causal therapy whenever possible. The acute attack is best treated by appropriate doses of ergotamine tartrate, except in cases of organic vascular disease.

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21. *Ménière's Disease*

JOSEPH HARKAVY

THE cardinal symptoms of Ménière's disease are deafness, tinnitus and vertigo. The deafness may occur without tinnitus. The vertigo may be paroxysmal in nature, frequently of the "turning type," and is very often accompanied by nausea, vomiting and nystagmus.

Classification

In the light of recent studies, Ménière's disease may be subdivided into (1) "symptomatic Ménière's syndrome" which may be caused by (*a*) interference with the function of the eighth nerve induced by degenerative vascular disease or lesions at the cerebellopontine angle, or (*b*) chronic adhesive processes in the tympanic cavity or obstruction in the eustachean tube; (2) so-called "idiopathic Ménière's syndrome," believed to be due to increased secretion and/or delayed resorption of the endolymph in the endolymphatic space of the inner ear where cochlea and vestibule are in direct communication. The resulting hydrolabyrinth leads to cochlear and vestibular dysfunction, with the development of the characteristic symptoms of Ménière. According to various observers the factors implicated in the evolution of the labyrinthine hypersecretion may consist of a metabolic dyscrasia due to retention of sodium on the one hand, and vascular disturbances in the internal ear on the other. In the past the latter were considered to be in the form of hemorrhages. Such a theory no longer finds universal support. In its stead the hydrolabyrinth is regarded by Atkinson[1] as a consequence of vasomotor influences characterized by primary vasodilatation and primary vasoconstriction. Additional causes may be arteriosclerosis, vascular toxic labyrinthitis secondary to focal infection, and systemic diseases such as syphilis, influenza, malaria, and virus infections.

Pathologic Physiology

The underlying mechanisms responsible for the development of vasodilatation have been ascribed to allergy, histamine sensitivity and to the sequelae of vasoconstriction.

Allergy was invoked to explain the exudative reaction in the labyrinth in view of the fact that certain allergic reactions are characterized by tissue edema. Hypersensitiveness to various allergens can only be proven in a small percentage of patients suffering with symptoms of

Ménière's disease, whereas in the larger number presenting the same symptoms no such evidence can be obtained with the present methods of investigation.

Atkinson,[1] on the basis of the theory that histamine or histamine-like substance mediates allergic reactions, employs skin reactions to histamine to indicate the existence of hypersensitiveness. In view of his observations that the symptoms of the cases reacting positively to the test dose of histamine are influenced favorably by the repeated injections of this substance, this investigator concludes that such patients are allergic individuals, sensitive to histamine. However, effects due to histamine that may be liberated by any means other than through an antigen-antibody mechanism are not allergies by the presently accepted definition of the term (see p. 16).

In contrast to these concepts is the explanation offered for the development of labyrinthine hypersecretion in patients whose symptoms are presumed to be due to primary vasoconstriction. The argument advanced is that vasoconstriction induces anoxemia of the vessel walls as a result of which vasodilatation supervenes with increased capillary permeability and edema similar to that observed in Raynaud's syndrome. The cause for the vasoconstriction is not known.

Support for the contention that increased labyrinthine pressure is responsible for Ménière's symptoms is gained from the histologic findings. In the autopsy examination of the temporal bones of three patients Hallpike[2] found "a gross destruction of the endolymphatic system together with degenerative changes in the sensory elements." Lindsay[3] reported the neural elements in his cases well preserved in contrast to the great distortion of the membranous structures. The normal column of perilymph from the oval window to the round window had been broken up or distorted by the dilated saccule and cochlear duct at the expense of the perilymphatic cistern and vestibular scala. This apparently accounted for a disturbance in the function of the fluid column. A striking feature was the dilatation of the saccule which herniated into the small end of the horizontal semicircular canal in some instances, while in others herniation from the utricle to the ampullae of the semicircular canals, with distortion of the outer wall of the ampullae, seems to offer a possible explanation for the disturbance of vestibular function. According to Lindsay[3] impairment of vestibular response in late stages of the disease could be attributed to permanent distortion of the ampulla, whereas transitory distortion would account for attacks of vertigo and perhaps a temporary decrease in the caloric response.

Etiology

Having ascribed the mechanisms responsible for the symptoms of Ménière's disease to allergy, histamine sensitivity and the sequelae of vasoconstriction, these three possible etiologic factors will be further discussed.

Allergy. Dohlman[4] was able to demonstrate experimentally vestibular disturbances in guinea pigs following anaphylaxis. These he localized in the central vestibular zone of the medulla oblongata. While such a mechanism may not be responsible for similar symptoms in man, this does not exclude the possibility that the labyrinth may be a shock tissue involved in human hypersensitiveness.

Supplementing the theoretical considerations is the clinical observation that a small group of patients with Ménière's disease give evidence of hypersensitiveness to various allergens.

Duke[5] was one of the first to report cases of Ménière's disease due to sensitivity to pears, spinach, plums, vinegar and wine. Attacks could be induced by the deliberate feeding of the offending foods or by the injection of their extracts. Patients sensitive to milk, eggs, wheat and beef have also been recorded by Dohlman and others. Following the omission of the offending foods these patients became free of symptoms and suffered exacerbations on eating them again. Various other types of hypersensitiveness have been reported by Rowe and Richet,[6] Balyeat,[7] Dean,[8] Adelsberger and Munter.[9] Malone[10] recorded two cases in which orris root and house dust were the incriminating allergens. The presence of angioneurotic edema in association with the Ménière's syndrome in patients described by Dederding,[11] as well as Wilder and Urbach,[12] suggested a similar reaction in the labyrinth.

In addition to the typical cases attributed to allergy there are others in which only some of the features described by Ménière may be present. These persons may be regarded as suffering from abortive or larval forms of the disease. It is conceivable that the series of nine patients reported by Criep[13] as "allergic vertigo," who were found sensitive to various foods and inhalants, belong to this category. Some of his patients in addition to vertigo manifested tinnitus, deafness and gastric disturbances.

Clinical Manifestations. The allergic person with Ménière's disease is relatively young, the average age of onset being thirty years. Women predominate in a ratio of eight to one. The patient frequently has a premonition of the oncoming attack several hours before its appearance. He may become irritable, experience a sense of fatigue and occasionally nausea. The hearing is decreased, the tinnitus increases, and severe headache supervenes, first on the side of the greatest impairment of hearing and later becoming more generalized. The patient experiences a sensation of "something bursting" in the head and the attack is on. It may last a half hour or longer and culminate with a vomiting spell. During the paroxysm the patient may break out into a cold sweat. The increased labyrinthine secretion leads to a "damping down of the whole cochlea causing increasing deafness involving all tones, deafness which precedes the attack and is relieved by it." In the later stages the persistent edema, whether induced by repeated allergenic stimulation or secondary to vasospasm, brings about degenerative changes in the cochlear nerve filaments resulting in progressive deafness of the nerve type affecting all tones. The simultaneous involvement of the one vestibule in this process alters its function and puts it out of balance with the other one on the opposite side. This gives rise to vertigo. At the conclusion of an acute attack the headache, tinnitus and vertigo subside with a gradual return to the status quo.

Histamine Sensitivity. As previously indicated, following the suggestion of Dzsinich and Galle,[14] Atkinson[1] uses intradermal tests with histamine as a substitute for routine tests with allergens in order to identify the so-called allergic person. This investigator finds that by injecting 0.01 mg. of histamine dihydrochloride intradermally, the patient sensitive to this drug, inferentially an allergic, develops a wheal 1 to 1.9 cm. in diameter with a surrounding flare of 5 to 6.4 cm. together with a pseudopod 2 cm. or more in length. In contrast to this, the wheal in the insensitive or non-allergic person is but 0.8 to 1.3 cm. in diameter with smooth contours surrounded by a flare of only 3 to 3.8 cm. The latter begins to fade in ten minutes and disappears in twenty minutes, whereas in the histamine-sensitive person the pseudopod, which is absent in the insensitive person, does not start to fade until the end of fifteen to twenty minutes or longer. Twenty per cent of the patients with Ménière's disease have been found to be sensitive to histamine by this technic. At times attacks could be induced with the test dose described, whereas repeated injections of histamine were followed by freedom from attacks.

Vasoconstrictive Group. The majority of patients whose symptoms have been attributed to primary vasoconstriction are persons of forty years of age and upwards. In addition to these, however, there is a small number of persons, more often women than men, in whom the disease begins in the early twenties. In this group there is no demonstrable allergy and no evidence of sensitivity to histamine. In patients who develop their symptoms during the late fifties and sixties, the vasospasm is regarded as the result of localized degenerative vascular lesions. The assumption that the manifestations in the others are due to vasoconstriction is based on the beneficent therapeutic effect of vasodilator drugs such as amyl nitrite and nicotinic acid on the one hand, and the precipitation of attacks, especially vertigo and nystagmus, with vasoconstrictor drugs such as epinephrine on the other.

The symptoms in the younger patients may frequently be induced by exposure to cold or emotional disturbances. They are distinguished by the frequency of exacerbations and the progressive nature of the deafness and tinnitus which may be resistant to treatment. The vertigo may be sudden, transient or recurrent, culminating in a major or overwhelming attack which may be so devastating as occasionally to throw the patient to the ground, causing serious injuries. Following such a paroxysm the impairment of hearing is greater and frequently bilateral. The tinnitus may also be severe. The disturbance in equilibrium, which may ensue, can last three to four days. These sequelae are in striking contrast to the course in the allergic group in which the attacks are followed by definite improvement in the patient's symptoms.

Diagnosis

In the patient with Ménière's syndrome it is necessary first of all to exclude (1) Ménière's neurosis, (2) local disease of the middle ear, such as a chronic adhesive process of the tympanic cavity or obstruction of the eustachean tube, (3) organic disease of the brain which interferes with the function of the eighth nerve.

The neurosis is suggested by the personality of the patient, the exaggeration of his symptoms, the finding of normal hearing, the absence of nystagmus and normal neurologic findings.

Organic disease of the ear or the brain is determined by reference to proper consultants.

After ascertaining that the manifestations are not due to any such conditions as the above, other factors which may possibly be responsible for the presenting symptoms such as allergy, histamine sensitivity or metabolic disturbances should be investigated.

To establish a diagnosis of allergy several of the usual criteria such as family history of hypersensitiveness, a personal history of associated allergic manifestations, i.e. asthma, hay fever, eczema, a record of clinical sensitivity to foods and drugs, blood eosinophilia and the demonstration of positive skin tests to various allergens, if possible, are to be sought.

To distinguish the histamine-sensitive, or so-called "allergic individual," from the insensitive or "non-allergic" it is necessary to adhere rigidly to the criteria laid down as to the size of the histamine wheal and the presence of pseudopods. This is, however, contrary to my experience with allergic patients in whom many variations are encountered in the manner in which they react to intradermal injection of allergens as well as to histamine. To differentiate allergic from non-allergic individuals on the size of a histamine wheal reaction alone is, in my opinion, not only difficult but entails the risk of overlooking many whose symptoms may be due to some type of hypersensitiveness capable of determination by the routine method of testing or by elimination of offending allergens. This may even apply to cases which are regarded by

Atkinson as belonging to the so-called vasoconstrictive category and which constitute the major proportion of patients with Ménière's disease.

Treatment

Control of symptoms in the *allergic patient* is achieved by eliminating the exciting agents or by the usual procedures of treatment by injection when indicated.

Therapy of the *histamine-sensitive group* consists of the subcutaneous injection of the initial intradermal test dose of 0.01 mg., which is gradually increased twice or at most three times weekly to the limit of tolerance to a maximum of 1 mg. or less. The final dose is administered once a week for a month. A second course of treatment after a three-month interval is frequently given. Attacks induced by overdosage of histamine are readily controlled by epinephrine injections. According to the available reports not only the paroxysmal vertigo but also the associated headaches disappear completely or become infrequent and mild with this form of therapy. Deafness and tinnitus, however, are not always so readily controlled, inasmuch as relief from these symptoms depends on the duration of their existence. Long-standing deafness and tinnitus obviously associated with irreparable organic damage do not yield to histamine treatment. Twelve of fourteen histamine-sensitive cases treated by Atkinson with this method were relieved, one improved, and one relapsed.

Vasoconstrictive Group. The most satisfactory treatment of the vasospastic group has been found in the intravenous administration of nicotinic acid. The initial dose consists of 25 mg. and is gradually increased to the limit of tolerance. This is continued for a month or more and ultimately slowly decreased till a maintenance dose is reached which varies in each individual case. Oral administration may also be used in favorable circumstances. The mouth dose of nicotinic acid is from 50 to 100 mg. Of forty-nine non-histamine-sensitive cases treated by Atkinson with nicotinic acid, twenty were relieved, twenty-five improved and four relapsed.

Sheldon and Horton,[15] without separating their cases into the vasospastic and histamine-sensitive cases, report that they were able to abort the acute symptoms of Ménière's disease by the intravenous administration of histamine alone. They employ a solution of 1 mg. of histamine base in 250 ml. of physiologic saline solution. This is injected at the rate of 50 to 60 drops per minute by the gravity method, during a period of one and one-half hours.

Metabolic Disturbances. In the treatment of cases of Ménière's disease which Mygind, Dederding[16] and others believe are due to a disturbance of water and salt metabolism, a dehydrating regimen is advocated. Furstenberg, Lashmet and Lathrop,[17] who present evidence to the effect that sodium salt retention is of greater significance in the production of the symptoms than water retention, recommend a low sodium diet supplemented by periodic administration of ammonium chloride. Opposed to these findings are the studies by Talbott and Brown[18] of the acid-base constituents of the serum in forty-eight patients with Ménière's syndrome. These investigators did not find any constant variations from the normal, although in four instances in blood taken during an acute attack, there was an increase in the concentration of serum potassium and a decrease in the serum sodium. Large doses of sodium salts administered intravenously or orally in order to augment the serum sodium failed to cause an exacerbation of symptoms in the cases thus treated. Talbott and Brown conclude that neither hydration nor alkalosis, nor an elevated serum sodium, is a necessary accompanient of Ménière's syndrome. They found that treatment of these patients with high potassium intake and otherwise normal diet resulted in "impressive" clinical improvement. Walsh and Adson[19] in treating patients with Ménière's syndrome employ 9 mg. of potassium nitrate daily for three days, with free intervals of two days, together with a low sodium diet. In cases where the medical approach fails or the loss of time from work as well as prolonged medical care are not feasible, these investigators advise section of the vestibular portion of the acoustic nerve.

Summary

Analysis of the foregoing observations indicates that with the exception of those cases in which an organic lesion is the actual cause of Ménière's syndrome, the mechanism responsible for the development of this clinical entity may be considered to be a vascular disturbance which brings about edema and distention of the labyrinth. This may be in the nature of a primary vasodilatation via an allergic mechanism, in which liberation of H-substance brings about increased capillary permeability, or it may be secondary to an initial vasospasm, the cause of which is still obscure. While Myging, Dederding and others on the basis of favorable therapeutic effects with dehydrating and low salt diets regard the edema as dependent on a disturbance of salt and water metabolism, there is no decisive evidence for this in the studies of Talbott and Brown. Whether the electrolyte imbalance represents an effect rather than a cause cannot be determined solely on the basis of results of therapy. Moreover, Brunner[20] questions whether the results with the low salt and dehydrating regime as reported are actually due to the treatment, to the loss of labyrinthine function, or to spontaneous remission either temporary or permanent.

Similarly the control of symptoms by means of "histamine desensitization" so-called cannot be accepted as evidence of an existing allergic state; neither can the favorable action of nicotinic acid in the so-called vasospastic patients be regarded as a negation of an underlying allergic condition. That both vasodilatation and vasospasm may be induced by H-substance released through antigen-antibody interaction has been demonstrated experimentally as well as clinically. That tissue edema may be brought about by liberation of H-substance through cholinergic impulses originating in the central nervous system as a result of exposure to cold and heat has been shown by Grant, Pearson and Commeau[21] in experimental urticaria. That such a mechanism rather than an immunologic one may account for the manifestations in the younger, so-called vasoconstrictive group of patients whose symptoms follow exposure to cold or heat, physically or emotionally induced, cannot therefore be excluded as a possibility.

While not disregarding the importance of favorable symptomatic forms of treatment as advocated by various students of this problem, it seems evident that the therapeutic control of the symptoms does not necessarily clarify the nature of the etiologic factors involved, nor effect their elimination. To determine the cause by every possible method must therefore be the goal in each individual case, but this usually is not at present attainable.

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Section VI

ALLERGY OF THE CARDIOVASCULAR SYSTEM

22. Cardiovascular Allergy

JOSEPH HARKAVY

In the attempt to explain the origin of certain lesions involving the vascular system and the heart with the resulting symptom complexes, the concept of sensitization has been invoked. Data on the immunopathology are obtained from studies of tissue reaction in experimental anaphylaxis and from clinical observation.

Immunopathology of Vascular Allergy

In Experimental Animals. It has been generally accepted that anaphylaxis in the lower animal is the prototype of human hypersensitiveness. The tissue primarily involved in this reaction, which is usually referred to as the "shock tissue" or "organ," varies in different animals. The question as to what constituent in the shock organ is selectively affected by specific antigenic stimulation has been the subject of numerous investigations. The possible points of impact have been considered to be the smooth muscle, the contractile elements of blood vessels, the vascular endothelium, connective tissue and/or the nerve endings within the enumerated tissues. The contraction in vitro of the sensitized isolated guinea pig uterus in response to the application of a specific antigen serves as evidence that the smooth muscle is the reactive element. The spasm of the pulmonary arteries in the anaphylactic rabbit and of the hepatic veins in the dog following antigenic stimulation may also be attributed to contraction of the smooth muscle in the walls of the anaphylactic vessels.

However, Manwaring, Chilcote and Hosepian,[1] as well as Petersen and Levinson,[2] have shown that besides the muscle a prominent role is played by the capillary endothelium. The latter may be so damaged in the anaphylactic process as to permit the free passage of the erythrocytes. Abell and Schenk,[3] who studied the effect of horse serum introduced into the moat of the ear chamber in rabbits sensitized to horse serum, noted the contraction of the arterioles, with stoppage of the circulation, an increased tendency of leukocytes to adhere to the endothelium and migration of leukocytes in large numbers through the walls of capillaries and vessels. Reinjection of horse serum into the moat resulted in extravasation of erythrocytes and destruction of the endothelium.

The observations by Froelich[4] and Roessle[5] of the local anaphylactic reaction or Arthus phenomenon in the mesentery of the sensitized frog following local application of hog serum lend further support to the vascular theory of the reaction due to hypersensitiveness. They describe capillary stasis characterized by engorgement of these vessels with plasma and diapedesis of leukocytes accompanied by distinct edema of the contiguous nerves. The Arthus phenomenon produced by sensitization with various proteins such as horse serum, egg white, etc., is also characterized by edema in the guinea pig, and in the rabbit by severe necrosis. The necrotic lesion according to Menkin[6] is marked by increased permeability of the capillaries, outpouring of fibrinogen into the tissue spaces with deposition of fibrin and thrombosis of the lymphatic capillaries and small veins, conditions which insure the local fixation of antigen.

The studies of Cannon, Walsh and Marshall[7] of the acute local anaphylactic inflammation of the lungs in the egg-sensitized rabbit following intranasal instillation of purified egg albumin showed that there was an acute pneumonitis characterized by edema, alveolitis, bronchitis and pneumonic consolidation. The perivascular lymphatics were dilated and contained many erythrocytes and there were occasional areas of acute arteritis and phlebitis as well as mural thrombosis. These authors concluded that the primary effect of antigen-antibody reaction in the lungs was an increased capillary permeability, followed later by severe vascular injury. They regarded the extent of the reaction as dependent "upon the varying intensities of the antigen-antibody union."

The vascular network in the three-day-old chick embryo, which has been shown by Szepsenwohl and Witebsky[8] to contain Forssman's antigen, goes into shock following the application of Forssman's antiserum. This is characterized by the shrinking of the vascular network, the turning about of the embryo which sinks into the yolk followed by a total standstill of the heart. A similar sequence of events occurs, as shown by Wittich,[9] during the anaphylactic shock in eighteen-day-old chick embryos. These observations strongly support the concept that the primary phase following sensitization may be essentially vascular in nature.

In Man. While the smooth muscle is fully recognized as one of the primary sites in the anaphylactic reaction in many of the lower animals, there is no experimental or histologic proof that such is the case in man. In the latter, according to Lewis[10] and Dale,[11] the allergic reaction is the result of the interplay between antigen and antibody on or within the cell which leads to the liberation of H or histamine-like substance causing increased vascular permeability and edema. This would imply that in a capillary the endothelium is the primary point of contact with the antigen. Thus the wheezing respiration in asthma could be due to edema of the bronchial mucosa. Yet the narrowing of the bronchi during an asthmatic attack, demonstrable by bronchography, and the contraction of hollow viscera such as the pylorus or intestine as visualized roentgenographically following the ingestion of sensitizing substances, would suggest that in addition to edema of the mucosa, the muscle fibers also participate in the response. Whether this muscle spasm is a secondary functional disturbance due to reflex irritation of the sympathetic nerves or the result of chemical substances released in the edema fluid is unknown.

Typical of the simplest vascular reactions in man is the urticarial wheal which may be induced clinically by the intradermal injection of a specific allergen. Histologically this is characterized by edema and the mobilization of eosinophils which reach their maximum within the hour and subsequently give way to a non-specific round cell and leukocytic infiltration. An expression of a more marked endothelial reaction is observed in purpura following drug, food or bacterial hypersensitiveness where a dissolution of the capillary wall is followed by diapedesis of erythrocytes into the surrounding tissue. A striking example of this is found in the clinical condition known as Henoch's purpura. When bacterial allergy predominates, inflammatory reactions of the vessel wall may attain various degrees of intensity depending upon the degree of allergenic stimulation. A response which is vastly accelerated is frequently designated as a hyperergic reaction.

Factors in Development of the Vascular Shock Tissue

Heredity. The conditions leading to the development of the vascular system as a shock organ are similar to those which obtain in bronchial asthma or eczema, or other allergies. The first is the constitutional predisposition. This is governed by genetic factors which account not only for the inheritance of the allergic state but also for the character of the shock tissue. Thus for example, the child of an asthmatic parent is apt to develop respiratory allergy, while another in whom gastro-intestinal or skin allergy prevails may become subject to similar disturbances. This may also be true in cases with cardiovascular disease, where records of family trends to diseases of the heart or blood vessels are very often available. There may be many patients with vascular manifestations in whom no such familial background exists. This is also the case in asthmatics in whom a family history of allergy is obtainable in 50 per cent of the individuals. Nevertheless, patients with negative histories may display clinical symptoms identical with those whose family records are positive. It has likewise been shown that so-called normals, depending upon the degree of their susceptibility and the character of the antigenic stimulation, can become sensitized by foreign proteins with the production of antibodies, "reagins," similar to those seen in the constitutionally allergic or "atopic" individual. The difference between the two, however, is that the latter shows an augmented tendency towards polyvalent sensitivity with multiple clinical manifestations, as well as greater concentration of reagins in contrast to the so-called normal.

Non-specific Agents. Aside from any inherited predisposition, the development of sensitivity in the so-called normal as well as in the atopic individual may be brought about by a number of non-specific agents of chemical, physical or bacterial nature. Pathophysiologic changes wrought by such excitants may so alter reactions of the affected tissues that they become more readily sensitized by allergens to which they were previously impervious. This is best illustrated by such experiments as the development of hyperergic reactions in the cardiovascular system of the sensitized animal following administration of epinephrine, caffeine or alcohol (Knepper and Waaler[12]), or in joints and adjacent tissues after refrigeration and trauma (Vaubel,[13] Lasovsky and Kogan[14]). A similar relationship may exist between tobacco and the cardiovascular system. Here the pharmacologic action of nicotine may, in predisposed individuals, render the vascular tissue more vulnerable to the allergenic effects of tobacco by virtue of the anoxemia of the endothelium brought about by the vasoconstrictive effect of nicotine.

Bacterial Toxins. The role of bacterial infection in creating a shock tissue is illustrated by the Shwartzman[15] phenomenon. In 1926 Shwartzman demonstrated that an intradermal injection of Eberthella typhosa filtrate into the skin of a rabbit, followed in twenty hours by an intravenous injection of the same toxic filtrate, produces a severe hemorrhagic necrotic lesion at the site of the previous intradermal injection. Histologically, the lesion consists of a destruction of all cells in the involved area, intense hemorrhage into the surrounding tissues, and platelet thrombosis of small vessels. Various other microorganisms such as the colon-dysentery group, Hemophilus influenzae, Hemophilus pertussis, Neisseria intracellularis, Diplococcus pneumoniae, Streptococcus (hemolytic), Neisseria gonorrhoeae, Treponema pallidum, Mycobacterium tuberculosis, etc., likewise elaborate soluble toxins which produce the typical phenomenon.

In animals prepared with one type of bacterial toxin a similar result may be attained by the intravenous injection of toxins derived from heterologous microorganisms as well as unrelated antigen-antibody complexes. For example, if the skin area is prepared by the local introduction of a typhoid culture filtrate, a necrotic lesion can be evoked by intravenous injection of a potent meningococcus, pneumococcus or streptococcus filtrate, or by foreign proteins such as egg white or horse serum with their respective antiserums.

This indicates that various bacterial toxins as well as unrelated antigen-antibody complexes are capable of producing the same type of cell injury in spite of the fact that they differ from each other, both chemically and biologically.

While the phenomenon itself may be elicited by a heterologous filtrate, inhibition of the phenomenon can be carried out only by specific immune serum.

Although the mechanisms of sensitization have been studied to a certain extent in conjunction with diseases of the skin and the respiratory system, very little has been done in investigating their role in relation to the cardiovascular system. In dealing with diseases affecting the heart and blood vessels, the criteria established for the diagnosis of recognized allergic diseases must serve as a point of departure. Thus it is highly important to follow the development and course of cardiovascular involvement as it appears in the allergic person whose constitutional background is so significant in his reactions to disease, as well as in the so-called normal individual capable of acquiring sensitization. Here, as in asthma, if an allergic mechanism is operative in the evolution of symptoms, the process should be both reversible and irreversible, and the exciting cause, as in other forms of allergy, discovered in foods, inhalants, drugs, bacteria or combinations of any of these.

Cardiovascular Reactions to Tobacco

Since the early studies of allergic manifestations concerned themselves with the observations on reactions to non-living foreign proteins such as pollens, inhalants or foods, it was deemed advisable in the study of allergic reactions of the vascular system to pursue similar steps. The most common allergen whose clinical effects on the cardiovascular system has been under discussion for many years is tobacco.

The response of living organisms to so complex a substance as tobacco demands the consideration of (*a*) the pharmacologic reactions to nicotine and various substances contained in smoke and (*b*) allergy to the pharmacologic agents themselves.

Pharmacologic Reactions. The effect of smoking several cigarettes has been shown by Maddock, Malcolm and Coller,[16] Lampson,[17] Mann[18] and others to result in a decrease of skin temperature of the fingers and toes due to vasoconstriction and diminution in the blood flow. Increase in blood pressure and pulse rate to the same degree was obtained by nicotine injected intravenously in amounts theoretically absorbed in the smoking of one or two cigarettes. The character of the response was shown to be identical in both men and women. Nor was there any difference noted in this respect in normal persons and those suffering from peripheral vascular disease such as thrombo-angiitis obliterans. That these results were brought about through the effect of nicotine on the autonomic nervous system was clearly demonstrated by Maddock[16] and collaborators by anesthetizing the nerve supply to the tested area and thus abolishing the vasoconstrictor effect, as compared with the unanesthetized control sites.

Allergic Reactions. In view of the fact that normal persons without symptoms from tobacco may smoke as much as those who do develop symptoms and are subjected to the same nicotine effects, it is questioned whether the resulting pathologic reactions in the latter should be attributed solely to the pharmacologic action of smoking or nicotine. By analogy, the production of a fixed skin eruption in certain persons following the ingestion of phenolphthalein cannot be ascribed to its common pharmacologic laxative effect. It follows, therefore, that the untoward reactions from tobacco may be associated with some non-pharmacologic mechanism which renders some persons more vulnerable to its use than others. The mechanism which suggests itself most prominently is allergy. Inasmuch as current knowledge of even the simplest steps in the allergic reactions to foreign proteins does not embody sufficient information to elucidate all of the features involved, it is impossible at this stage in the study of so complicated a human response as that to tobacco to account adequately for the role of each of the participating factors.

Investigations of sensitization to nicotine tartrate in dilutions of 1:10,000 and 1:5000 carried out by Harkavy[19] as well as by Sulzberger[20] have thus far been negative. This may be due to inadequate methods of testing. Notwithstanding the negative findings, neither the sensitizing nor the pharmacologic influence of nicotine can be divorced from the appraisal of any clinical effects due to smoking. However, in order to differentiate the purely pharmacologic action of nicotine from that more intimately related to tobacco hypersensitiveness capable of objective analysis, investigations were carried out by means of direct skin tests with various tobaccos, passive transfer experiments and sensitization of animals with the tobacco extracts used in testing patients. These yielded the following results.

The Allergic and Anaphylactic Reactions to Tobacco.[19,20] Of 400 unselected normal smokers 32 per cent reacted to tobacco and to extracts of timothy or horse dander, and 9 per cent to tobacco only.[21] On a control group of 126 non-smokers,[22] having no family or personal history of allergy, a total of sixteen or 12 per cent reacted to pollens and tobacco. Nine and two-tenths per cent of this same group reacted to tobacco only. Green,[23] studying 100 normal smokers, found 13 per cent reacted to tobacco only; Romanoff and Rubin[24] observed 16 per cent of reactions to tobacco only in sixty-eight normal smokers and Trasoff[25] reported 17 per cent in forty normal smokers, three of whom were atopic.

A comparison between the incidence of tobacco reactions in smokers and non-smokers indicates there are twice as many positive skin tests to tobacco among smokers who also react to pollens and horse dander, as among non-smokers. This, of course, substantiates the generally recognized fact that repeated exposure to a given agent may be frequently followed by the development of skin reactions as well as circulating antibodies, indicative of sensitization. This is particularly the case in the atopic person. Since it is safe to assume that pollen-reacting persons who possess corresponding reagins in their serums are atopic, the frequency with which tobacco skin reactions are manifested by them may be attributed to their constitutional make-up. The sources of sensitization are to be found not only in smoking but also in the atmosphere which abounds with tobacco dust 365 days a year, a period much longer than the pollinating season. This may account for the finding by Peshkin[26] of tobacco skin reactions in pollen-sensitive children and the similar observations reported by Chobot.[27]

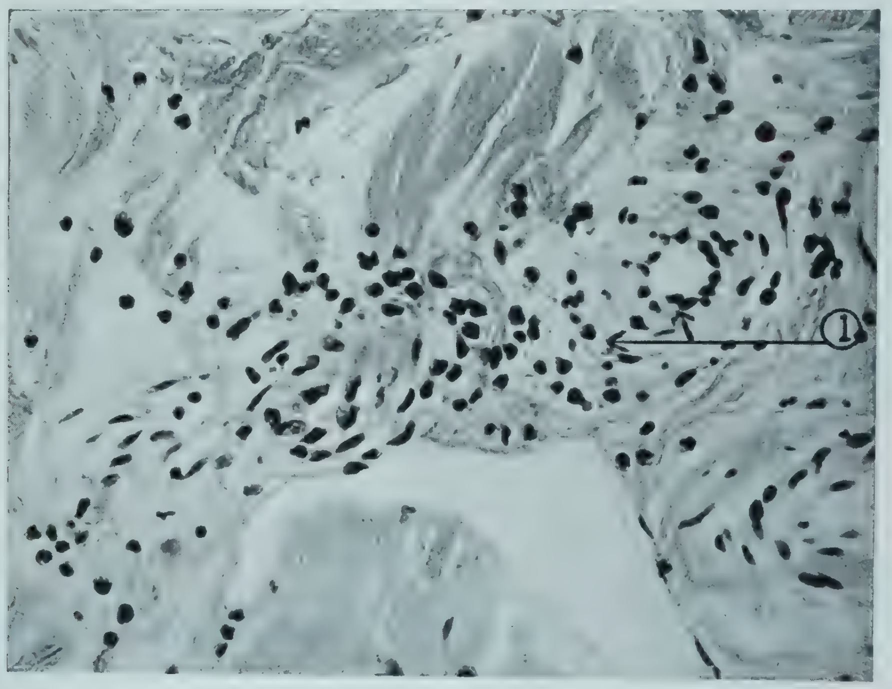

Fig. 30.—Biopsy of urticarial skin reaction to tobacco in a case of thrombo-angiitis obliterans. (1). Marked perivascular infiltration and invasion of the walls of arterioles with eosinophils. (Harkavy, J. Allergy, *9*:275, 1938.)

Whereas Chobot was unsuccessful in demonstrating tobacco reagins in the serum of the four patients whom he investigated by means of passive transfer, Peshkin was able to show tobacco as well as ragweed and timothy reagins by passive transfer in 72 per cent of fifty children who reacted to these substances by direct skin test. These findings are in accord with the observations of Harkavy,[28] Walzer,[29] Lounsbury and Oughterson,[30] and serve to substantiate the immunological specificity of the tobacco skin reactions. Further support for this is to be found in the investigations of Harkavy and Witebsky.[31] These indicated (1) that the tobacco reagins in cases manifesting multiple sensitization can be specifically absorbed by corresponding tobacco allergens; (2) that biopsy sections of the immediate urticarial response obtained from patients with thrombo-angiitis obliterans, coronary artery disease and migrating phlebitis, sensitive to the intradermal test with tobacco, disclosed a characteristic local eosinophilic reaction[28] (Fig. 30); and (3) that 33 per cent of rats injected intraperitoneally with the same tobacco extracts as

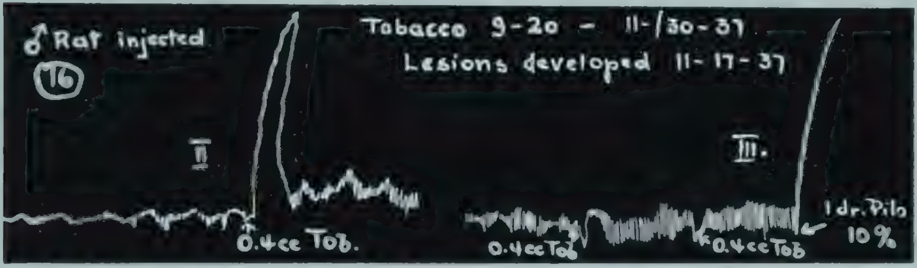

Fig. 31.—Exper. 2. Positive anaphylactic reaction of intestinal strip from Rat 16 sensitized to tobacco following the introduction of 0.4 ml. of tobacco extract. Exper. 3. Negative response of the same intestinal strip to repeated addition of 0.4 ml. of tobacco extract indicating that the gut had been desensitized to this substance. The continued capacity of the intestinal strip to contract is indicated after the application of one drop of pilocarpine.

employed in testing patients became sensitized to this antigen and developed gangrene of the toes.[32, 33] Evidence to the effect that these animals were actually sensitized to tobacco was presented by the positive anaphylactic reactions of the intestinal strips (Schultz-Dale technic). These observations indicate that the response to tobacco is a specific rather than an irritative reaction.

Cardiovascular Disease and Tobacco Allergy

Since the clinical bearing of any positive skin reaction regardless of its immunologic specificity is dependent on the presence of a shock organ responsive to the allergen, the question as to what shock tissues might be influenced by allergy to tobacco was investigated by testing with various tobaccos, pollens, etc., 319 ward patients presenting a variety of diseases and who were habitual smokers. Results of these tests disclosed that certain individuals who gave significant reactions to tobacco alone or in combination with pollens also manifested symptoms in which tobacco had long been suspected of playing a contributory or possibly an exciting role. The first group consisted of cases with thrombo-angiitis obliterans; the second, patients manifesting angina pectoris with and without coronary artery disease; and finally cases with gastric and duodenal ulcer. Inasmuch as patients with vascular disease were the primary object of these observations, a more detailed study was made of (1) peripheral vascular disease and (2) cardiac disease.

Peripheral Vascular Disease. *Thrombo-Angiitis Obliterans.* The symptom complex of thrombo-angiitis obliterans represents involvement uncomplicated by arteriosclerosis, the etiology of which is obscure, but in which the role of tobacco has been debated for fifty or more years. The typical disease occurs in men under forty-five years of age who smoke excessively. The youngest patient studied was under eighteen years of age.

A comparison of the findings in 140 patients with thrombo-angiitis obliterans tested with five tobacco extracts and extracts of ragweed, timothy and horse dander, with those in 400 normal control smokers revealed the following: 78 per cent of the thrombo-angiitis obliterans patients gave skin reactions to *tobacco only* varying from plus minus to four plus, as compared with 9 per cent to *tobacco only* in the normal unselected control smokers. Whereas 32 per cent of the control group of smokers reacted positively in various combinations to the simultaneous intradermal injections of ragweed, timothy, horse dander and tobacco extracts, only 10 per cent of the thrombo-angiitis patients gave reactions to the allergens other than tobacco. Forty-four per cent of ninety-five patients with thrombo-angiitis obliterans having skin reactions of one plus or more to tobacco also had demonstrable antibodies to tobacco in their serums by passive transfer. Sulzberger,[20] Romanoff and Rubin,[24] as well as Green,[23] in similar studies essentially confirmed these observations. Clinically, in every patient with thrombo-angiitis obliterans in whom tobacco was proven to play an exciting role, cessation of smoking was followed by arrest of the disease whereas exacerbations of symptoms invariably followed the resumption of smoking.

The following case is illustrative of vascular reaction in veins and arteries due to tobacco allergy in a reacting person.

P. F., aged thirty-three, was first seen in August 1941 with a history of pruritus since childhood. He smoked from twenty to thirty cigarettes a day, beginning at the age of fifteen. In 1935 he developed phlebitis in the left leg which gradually subsided. In 1938 numerous boils appeared on various parts of his body and lasted for nine months. In 1940 there was recurrence of the phlebitis followed by bilateral pulmonary infiltrations with effusion. These may have been an expression of migrating phlebitis of the pulmonary veins.

On admission to the Vascular Clinic at the Mount Sinai Hospital in July, 1941, in addition to migrating phlebitis there was evidence of thrombo-angiitis obliterans affecting the vessels of his left leg, and myocardial involvement. The electrocardiograph disclosed small Q 1, 2 and 4; T_4 was low, T_2 diphasic and T_3 isoelectric. He was tested on August 15, 1941, and showed skin reactions to Burley, Maryland, Virginia and Xanthis tobaccos; to ragweed and timothy pollens; as well as to various foods. Although he had never suffered from pollinosis he volunteered the information that his aunts and uncles had hay fever and asthma respectively. He was advised to stop smoking, with the result that the phlebitic nodules disappeared. The pruritus was controlled by the elimination of certain specific foods.

After the phlebitis had completely subsided he was retested with various tobaccos on August 20, 1941. Besides the immediate urticarial reactions to the tobaccos, he developed two days later delayed reactions to Burley and Virginia tobaccos together with new phlebitic nodules over the left ankle. The delayed reactions and the phlebitic areas disappeared completely on September 6, 1941. The question arose whether this sudden exacerbation of phlebitis indicated a reaction to the injected tobacco allergen. To confirm this he was retested September 10, 1941. This time he developed a moderate urticarial response to Burley, Maryland and Xanthis tobaccos and a delayed eczematous type of reaction to Virginia tobacco about 3 cm. in diameter. Concurrently a new phlebitic nodule developed over the left tibia, reached its peak September 23 and receded September 25. The delayed Virginia tobacco reaction disappeared September 26. The patient remarked that the phlebitis following the injection of tobacco extracts was of shorter duration than that after smoking.

He discontinued the use of tobacco completely and became free of all symptoms. The electrocardiogram gradually returned to normal. When last seen in November 1943 he had not had a recurrence of phlebitis. Although the vessels of his left leg, with the exception of the posterior tibial, were closed, he was doing a full day's work without any discomfort.

The demonstration of positive skin tests as well as antibodies to tobacco in the serums of patients with thrombo-angiitis obliterans and migrating phlebitis, and the clinical improvement as noted in the arrest of the progress in the disease following discontinuance of the use of tobacco, serve to satisfy the basic postulates of the allergic mechanism. These findings paved the way for investigation of other clinical expressions of tobacco hypersensitiveness such as borderline cases of thrombo-angiitis obliterans, i.e., patients whose vascular symptoms begin between the age of forty to fifty-five and in whom there may be an associated early arteriosclerosis; and patients with peripheral vascular disease due to arteriosclerosis, suffering from intermittent claudication.

Borderline Cases of Thrombo-Angiitis Obliterans. Fifty-eight per cent of the borderline cases of thrombo-angiitis obliterans and 45 per cent of patients with peripheral arteriosclerosis and intermittent claudication reacted to tobacco. In contrast, however, to the complete arrest of the disease process in the typical cases of thrombo-angiitis obliterans under forty-five years of age following cessation in the use of tobacco, the final outcome in the borderline cases of thrombo-angiitis obliterans as well as those with peripheral arteriosclerosis, despite symptomatic relief following elimination of smoking, depended on the extent and rapidity of progress of the underlying degenerative process.

Cardiac Disease. *Cardiac Arrhythmias.* In a series of cases observed over a period of several years, tobacco hypersensitiveness demonstrable by positive skin reactions and clinical tests was found to be the primary cause in the production of various types of cardiac irregularities such as extrasystoles, tachycardia and auricular fibrillation. These symptoms would appear shortly after smoking, and in some instances within twenty-four to thirty-six hours. They would persist as long as the patient smoked. After the withdrawal of tobacco these various disturbances disappeared completely only to recur whenever the patient resumed smoking.

Angina Pectoris and Coronary Artery Disease. The question of tobacco in relation to certain types of angina pectoris and coronary artery disease has been of interest to the clinician for many years. The term tobacco angina is frequently used in the literature to indicate precordial pain which appears in patients whose symptoms originate in smoking. Yet the mechanism involved in the production of this symptom complex has been obscure. The possibility that the explanation for this condition could be found in tobacco hypersensitiveness was therefore investigated in 100 patients with angina pectoris and coronary artery disease who were heavy smokers. It was found that about 44 per cent of these patients gave positive reactions to tobacco. Out of this group the serums of fourteen patients were selected for passive transfer; eleven or 71 per cent had demonstrable passive transfer reactions to tobacco. The positively reacting patients seemed to represent a relatively younger group of smokers, their age averaging about forty-five years. Inquiry disclosed family or personal histories of allergy such as asthma and hay fever in 33 per cent. This contrasted with 10 to 12 per cent in a group of 140 cases of thrombo-angiitis obliterans and 25 per cent obtained in a group of 400 normal unselected control smokers in the general population.

The relatively high incidence of constitutional stigmata of allergy in cases with coronary artery disease is striking. It suggests the possibility that in such individuals the coronary vessels and myocardium constitute the shock organ and that abnormal reaction in these tissues may be the result of hypersensitiveness to various foreign substances. However, before attributing an allergic etiology to the cardiac involvement in any given case it is imperative to exclude all other possible causes. *The finding of positive skin tests to tobacco in a patient with coronary artery disease is in itself insufficient ground for the conclusion that tobacco is responsible for the manifestations. Positive reactions assume etiologic significance only if the elimination of smoking is followed by relief and its resumption by exacerbation of symptoms.* Since the removal of one exciting factor does not preclude the operation of other agents in the elicitation of reactions in one and the same shock organ, one need not be surprised if there is a recurrence of anginal attacks as a result of other causes long after cessation of smoking in a patient whose heart had previously responded symptomatically to tobacco sensitization. Polyvalent sensitivity, just as in any other allergic condition, may also play a role in attacks of angina pectoris of allergic origin.

A typical example of angina pectoris due to tobacco allergy in an atopic individual who also manifested sensitivity to pollens and foods is illustrated by the following case.

A forty-three-year-old man with an allergic background was first seen in 1939. He had an episode of severe angina pectoris while smoking in April 1939, with electrocardiographic evidence of inversion of T_1 and T_4, and semi-inversion of T_2 suggestive of anterior wall infarction. He also complained of various gastro-intestinal symptoms and attacks of tachycardia after eating certain foods. Study disclosed that these shock tissues were influenced by sensitivity to foods, pollens and inhalants including tobacco. There was a striking affinity between some of these allergens and the specific shock organs. With the omission of smoking, the cardiac manifestations as well as the electrocardiographic changes returned to normal within four days. Exclusion of offending foods led to the disappearance of the gastro-intestinal symptoms and the few remaining possibly "reflex" cardiac manifestations. Immunization with pollen extracts prevented a recurrence of hay fever.

Cardiovascular Disease from Agents Other than Tobacco

Peripheral Vascular Disease. *Migrating Phlebitis Due to Food Allergy.* I have observed two such cases which were due to fish. L. Connor reported a case with idiosyncrasy to fish and shellfish, the consumption of which was followed by redness, tenderness and swelling along some part of the course of the internal saphenous vein of one or both legs. Abstention from fish caused complete disappearance of the symptoms.

Migrating Phlebitis in Association with Infection. The occurrence of migrating phlebitis in association with syphilis, tuberculosis and rheumatic fever has been frequently observed. This may be regarded as representing reactions in veins caused by hypersensitiveness to the bacterial agents responsible for the underlying disease.

Cardiac Disease. *Cardiac Arrhythmias.* These are characterized by premature beats, simple tachycardia, paroxysmal tachycardia and auricular fibrillation in the absence of the usual diseases of the myocardium such as rheumatic fever, hypertension, arteriosclerosis, etc., and have been attributed to fatigue, sudden exertion, indigestion, alcohol, digitalis poisoning, infections and reflex vagus stimulation. Similarly, auricular fibrillation of obscure nature has been considered to be of "toxic origin." Since most of the predisposing factors enumerated, with the exception of digitalis, represent the daily influences in the life of the average man in whom no such dramatic cardiac arrhythmias supervene, the question arises whether there is not, in addition to the external agent, some constitutional factor responsible for the precipitation of such paroxysms. An answer to this problem was indicated in a study of a group of patients reported in 1938[34] which disclosed that hypersensitiveness to foods could be followed by various types of cardiac arrhythmias.

Case 1. A young man of twenty-six, with a family history of asthma, who had been subject to frequent attacks of vasomotor rhinitis, developed attacks of extrasystoles and palpitation. Study disclosed that lamb, or lamb in combination with cauliflower, cabbage, or lettuce, tomatoes and peas invariably induced tachycardia, the rate varying between 110 and 172, associated with premature auricular beats which lasted from several hours to two days. Removal of these foods from his diet was followed by freedom from the cardiac and nasal symptoms.

Case 2. A schoolteacher, aged thirty, with a positive family history of allergy was seen in November 1925 because of cardiac palpitation and sneezing. Electrocardiograms disclosed paroxysmal auricular tachycardia with premature auricular beats, varying between 130 and 210. The attacks disappeared for five years and were replaced by gastro-intestinal symptoms. In 1933 tachycardia returned and the intestinal symptoms subsided. Investigation disclosed that she was sensitive to inhalants, pollen and various foods. The major foods responsible for her cardiac symptoms proved to be chocolate and shellfish. Following ingestion of either of these, attacks of palpitation and on one occasion angioneurotic edema ensued. The heart symptoms usually occurred three days after ingestion of a particular food to which she was sensitive. Complete cessation of attacks resulted from abstention from the sensitizing foods.

Case 3. A sixty-eight year old female patient had been observed since the age of fifty-seven with attacks of angioneurotic edema and occasional attacks of colitis after ingestion of shellfish. In 1929 after eating a mixture consisting of oyster and lobster she developed an attack of auricular fibrillation. This subsided after six hours following a colonic irrigation. Between 1930 and 1940 she developed repeated attacks of angina pectoris and cardiac arrhythmias characterized by premature beats alternating with angioneurotic edema, or angina pectoris alone, whenever she ate shellfish or milk products. During these attacks her liver became enlarged and painful. Catharsis was followed by relief of symptoms. The last attack of auricular fibrillation followed the ingestion of milk in 1942. This was relieved within twenty-four hours by means of a colonic irrigation. She died in 1943 following virus pneumonia at the age of seventy-four.

Cases of tachycardia due to food hypersensitiveness have also been reported by Kern,[35] Mussio-Fournier,[36] Weil,[37] Luria and Wilensky,[38] Thomas and Post[39] and recently by Davidson et al.[40] Kern's patient was a woman of forty who had had attacks of tachycardia since the age of five. The interesting feature in most of the cases described was the frequent presence of other allergic manifestations which appeared coincidentally or alternately with the cardiac arrhythmias and tachycardias. These consisted of urticaria, angioneurotic edema, migraine, hay fever and asthma.

Angina Pectoris and Coronary Artery Disease. FOODS, DRUGS AND POLLENS. Various reports of angina pectoris due to food hypersensitiveness have been made by Werley[41] and von Eiselsberg.[42] Angina pectoris as a result of sensitization to salicylic acid was described by Shookhoff and Lieberman[43] in three cases. In two it was accompanied by urticaria. In a third instance in which severe anginal pain could be repeatedly induced following the ingestion of acetylsalicylic acid, the administration of 5 grains of this drug resulted in electrocardiographic abnormalities characterized by prolongation of the P-R interval and notching of S_2 and S_3 with inversion of T_3. These changes disappeared simultaneously with the cessation of the attack. They were controlled to some degree by injections of adrenalin.

A fourth case studied by these authors was that of a sixty-three-year-old man, asthmatic, sensitive to ragweed pollen, who had sustained a coronary occlusion in 1930 from which he recovered. In August 1932 he developed severe anginal attacks at the height of the ragweed season which were successfully controlled by isolating the patient in a room aerated by means of a pollen filter.

BIOLOGICALS. In 1942 Boas[44] recorded the case of a forty-six-year-old man who cut his finger and received tetanus antitoxin. After a week, a rash appeared associated with an attack of syncope and precordial pain. Seven days later another attack occurred followed by death. Autopsy disclosed coronary sclerosis with a recent myocardial infarction. A similar case was reported in 1938 in the *Journal of the American Medical Association.*[45] The possibility that serum sensitization was responsible in both these cases for the reaction in the coronary vessels which led to thrombosis and infarction of the heart muscle must be entertained. This concept is supported by the observations of Clark and Kaplan[46] as well as Rich[47] on the effect of serum sensitization on coronary and other vessels.

A second case studied by Boas was that of a young man of thirty-four who developed attacks of angina pectoris as a result of tobacco allergy. Cessation of smoking was followed by the complete disappearance of the symptoms. After an interval of two years the patient resumed smoking. This time (1934) he developed excruciating pain in the right great toe which was finally relieved by several intravenous injections of typhoid vaccine. He was free of symptoms until 1936 when he again began to smoke. This was succeeded by severe pain in the toes of the left foot as well as in the substernal area. It was decided to repeat the intravenous injections of typhoid vaccine. After one treatment he developed a chill followed by fever. Six hours later he experienced severe precordial pain which was relieved by morphine. The next day his blood pressure had dropped to 96 systolic and 48 diastolic while the heart rate, although of fair quality, was 100 beats per minute. The electrocardiogram was unchanged. He ran a typical course of cardiac infarction and made a good recovery. Two years later he appeared well and asymptomatic. This case may be regarded as illustrative of a young man in whom the coronary and peripheral vessels constituted the major shock organs.

PHYSICAL AGENTS. In 1932 Duke[48] reported a series of cases with angina pectoris, extrasystoles and tachycardia brought about by hypersensitiveness to heat and cold. Under ordinary circumstances the physical examination disclosed no cardiac abnormalities. The various arrhythmias and anginal attacks could be induced repeatedly by the application of heat or by effort in three cases, and cold in another. Some of these patients were also pollen-sensitive. They could be relieved by applying an agent the reverse of the one which caused the cardiac disturbances, and were benefited by treatment with the substance responsible for the attacks.

INFECTIVE AGENTS. Because of the importance of infection in cardiovascular allergic disease, this subject will be discussed more exhaustively under the following heading.

Cardiovascular Reactions to Infectious Agents or their Products

The fact that bacterial sensitization may bring about vascular changes of severity equal to or greater than those resulting from tobacco and food hypersensitiveness was suggested by the study of a special series of sixteen cases of bronchial asthma.[49, 50] In these patients, the simultaneous appearance of asthmatic attacks and abnormal cardiovascular reactions resulted from exposure to the same allergenic excitants. Four of the patients in this group died and came to necropsy. The clinical course, except for the degree and number of shock tissues involved, was similar in the entire series and was characterized by the following features.

In five of the sixteen cases there was a family history of allergy, while in seven, two of which came to autopsy, there was a personal history of hypersensitiveness. Each one of these patients had suffered from repeated winter colds and had developed chronic infection of the sinuses. The latter was regarded as the potential source of bacterial sensitization which could have played a role in the precipitation of the asthmatic attacks.

Bacteriology and Bacterial Allergy. In six cases in which an attempt was made to identify the bacteria involved, the observed cutaneous and systemic reactions to pneumococcus polysaccharides and autogenous vaccines prepared from the flora of the sputum and sinus washings seemed to suggest some *causal* relationship to the presenting symptoms. Thus examination of the sputum in Case 1 disclosed the presence of pneumococcus Type VI. Skin tests with the polysaccharide fractions of ten different types of pneumococcus according to the standard technic showed immediate positive reactions to the polysaccharides of pneumococcus Types V and XIV, but none for Type VI. Nevertheless, precipitins for Type VI pneumococcus and agglutinins for pneumococcus Type XIV were demonstrable in the blood serum. Eight hours later, reddish nodules similar to tuberculin reactions appeared in the areas injected with the polysaccharide substance of pneumococcus Types V and XIV, and the patient developed a severe generalized urticaria which lasted for three days.

Two other cases (patients 2 and 3), whose aspirated bronchial secretions contained pneumococcus Type V and III respectively, and Case 4 from whose sputum pneumococcus Type III was cultured, were tested with the same number of polysaccharide fractions and gave immediate positive reactions to the corresponding polysaccharide fractions of these organisms. Both precipitins and agglutinins for pneumococcus Types V and III were present in the serums of Cases 2 and 3. Twenty-four hours later, delayed inflammatory nodules appeared in these two patients at the sites of the previous immediate positive reactions and were accompanied by exacerbations in the asthmatic attacks. Patient 4, examined in the midst of an asthmatic paroxysm, was not studied serologically.

Inasmuch as 40 per cent of normal persons show an incidence of positive skin reactions to various polysaccharides of the pneumococci indicative of some previous infection with these organisms, the thought suggests itself that in these cases also some infection with these or related organisms may have played a sensitizing role responsible for the presenting symptoms, especially in view of the focal and systemic reactions which followed the intradermal injection of the polysaccharide fractions.

In patient 5 the intracutaneous injection of an autogenous vaccine derived from the sinus washings, consisting of Staphylococcus aureus A, Neisseria catarrhalis and non-hemolytic Streptococcus, and in Case 6 a vaccine containing Staphylococcus aureus A only, were also followed by systemic reactions. The former patient developed a severe asthmatic seizure together with anaphylactic-like shock, and the latter, pulmonary infiltration accompanied by fever, cough, generalized petechiae and ecchymosis in the left calf. These, as well as the urticaria in Case 1, were the external manifestations of a vascular response dependent upon hypersensitiveness to the injected bacterial products. Positive reactions to foods, pollens and inhalants were present in eleven of the sixteen patients. Only in seven were they found to be of clinical significance in conjunction with the bacterial hypersensitiveness.

Clinical Studies. *Pulmonary Lesions.* Bronchial asthma associated with pulmonary infiltrations was the cardinal manifestation in fifteen of the sixteen cases. The one exception was a patient who was hospitalized because of a brawny infiltration at the elbow and a hemorrhagic necrotic lesion in Scarpa's triangle. Study of this patient's blood disclosed 65 per cent of eosinophils. A biopsy of the lesion in the thigh also showed an extensive eosinophilic inflammatory reaction. After a week of hospitalization she developed a cough and pain in the chest which on x-ray examination revealed involvement of the lungs similar in every way to that presented by the other fifteen patients. The pulmonary lesions in the latter persisted throughout the entire period of asthma, receding gradually with the termination of the attacks. The nature and extent of the infiltrations were as a rule not determinable by physical examination, which was characterized either by presence of the usual sonorous râles associated with asthma, or by scattered crepitations accompanied by slight dullness in various parts of the chest.

Roentgenologically the pulmonary lesions in some of the cases consisted of a disseminated mottling, miliary and submiliary in appearance, resembling acinous or nodular tuberculosis, with rather blurred outlines. At times the infiltrations involved the apices of the upper lobes and then again the hilar regions, whence they radiated to the periphery and formed confluent patches at the bases suggesting lobar pneumonia. As they progressed downward from the upper lobes they seemed to follow the bronchial tree and spread in narrow plate-like homogeneous densities extending obliquely caudad and laterally. According to Hennel and Sussman[51] there was no evidence of atelectasis, calcification or cavity formation. Resolution of the pulmonary lesions was usually complete except for a few linear strands.

The character of the pulmonary infiltration and blood eosinophilia, together with the relatively few physical signs, was reminiscent of the clinical picture described by Löffler[52] under the rubric of "Transitory Pulmonary Infiltrations with Eosinophiles," also referred to as Löffler's pneumonia. However, a comparison of our cases with those reported by the Swiss clinician disclosed the following points of difference. Although the lesions in the lungs in both groups were migratory, they were of short duration in Löffler's cases, disappearing within three to eight days, whereas in our patients they persisted from three to twelve weeks. Some of Löffler's patients were incapacitated for one to three days only, manifesting moderate cough, fatigue and very slight temperature. In fourteen out of fifty-one of his cases, the pulmonary lesions were discovered accidentally on routine x-ray examinations. Except for an occasionally marked blood eosinophilia, the total white blood cell count was normal. None of these patients had any wheezing respiration. In contrast, our patients suffered with protracted asthma accompanied by temperatures ranging between 99° and 104° F. and had to be confined to bed for varying numbers of weeks with each attack. The pulmonary lesions persisted throughout this period and even sometime after the temperature had subsided. There was also marked eosinophilia, and the total white blood cell count in most instances was very high.

In addition to these manifestations, our patients developed reactions in various serous membranes, the myocardium, the gastro-intestinal tract, the kidneys, skin and nervous system. These were suggestive of a systemic response in which numerous shock organs, whose vessels had been sensitized, participated. The symptoms which developed as a result of the involvement of these tissues were as follows:

Eosinophilic Pleuritis. In eight of the sixteen patients, simultaneously with the asthma and pulmonary lesions, there appeared sterile pleural effusions which on examination showed a specific gravity of 1.015 and eosinophilia up to 90 per cent. At the same time electrocardiographic abnormalities developed affecting the auricular and ventricular complexes. These as a rule were not associated with any auscultatory or other clinical evidence of cardiac involvement in the early stages of the disease. In the majority of the patients in whom the asthma subsided, both the pulmonary infiltrations and the pleural effusions, as well as the electrocardiographic changes, returned to normal, only to recur with the reappearance of the asthmatic attacks.

Pericarditis and Peritonitis. In addition to the manifestations in the lungs, pleura and heart, some of the patients developed symptoms referable to the pericardium. The sudden appearance of a pericarditis in one case was followed by a temporary suppression of asthma and the presence of urticaria and polyarthritis suggestive of rheumatic fever, except for the persistence of a high blood eosinophilia. With the subsidence of the pericarditis the asthma returned. In the other cases which came to a fatal termination, the inflammation in the pericardium became chronic, and together with the progressive lesions in the myocardium gave rise to enlargement of the cardiac outlines, with various murmurs as well as irreversible electrocardiographic changes. Three of the patients developed signs and symptoms of constrictive pericarditis. This was followed by fluid in the abdominal cavity which proved to be sterile on culture and contained eosinophilic cells up to 100 per cent. The simultaneous presence of effusions in the pleura, pericardium and peritoneum in these cases suggested "Pick's Syndrome." The discovery of marked eosinophilia in the various exudates implied that the pathogenesis of the polyserositis was based on allergic reactions in the capillaries of the lining membranes which permitted the passage of eosinophils into the serous cavities.

Other salient features were polyneuritis in four patients and various skin lesions in the nature of urticaria, purpura, papular erythema and angioneurotic edema, and in one case subcutaneous nodules. Biopsies of the purpuric lesions disclosed edema and perivascular eosinophilic infiltration. The subcutaneous nodules revealed periarteritis nodosa.

Laboratory Data. Bronchoscopy in three of these cases disclosed pale swollen mucous membranes with mucoid secretions in which eosinophilia predominated. On culture the bronchoscopic aspirations yielded pure strains of pneumococci Types VI, V and III respectively. The sputum examinations of the other cases disclosed a variable flora consisting of pneumococci, Streptococcus hemolyticus, Streptococcus viridans, Staphylococcus albus, Neisseria catarrhalis, Borrelia vincentii, etc. Washings from the sinuses disclosed the presence of pneumococci in some cases, Staphylococcus aureus hemolyticus, Staphylococcus albus and Streptococcus viridans, Staphylococcus aureus and Staphylococcus citreus in others.

The blood counts were characterized by numbers of leukocytes ranging from a minimum of 7000 to a maximum of 10,000 and by the percentage of eosinophils ranging from 7 to 84 per cent. Bone marrow obtained by sternal puncture in three cases showed a marked increase of eosinophils. Blood cultures taken in five cases were reported to be sterile.

Course. Seven of the sixteen patients recovered from their attacks during the period of observation, and the lungs, pleura and heart returned to normal. The eighth patient developed chronic cardiac insufficiency and the ninth disappeared from observation. The remaining seven patients died. Four of these came to autopsy.

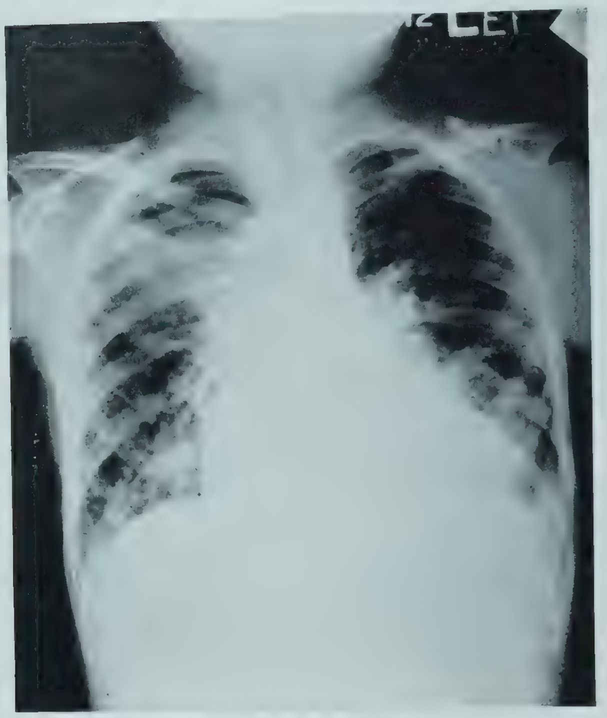

Fig. 32.—Case B. Infiltrations throughout both lungs, confluent in right upper and left lower bases. Heart enlarged. (Harkavy, J. Allergy, *14*:507, 1943.)

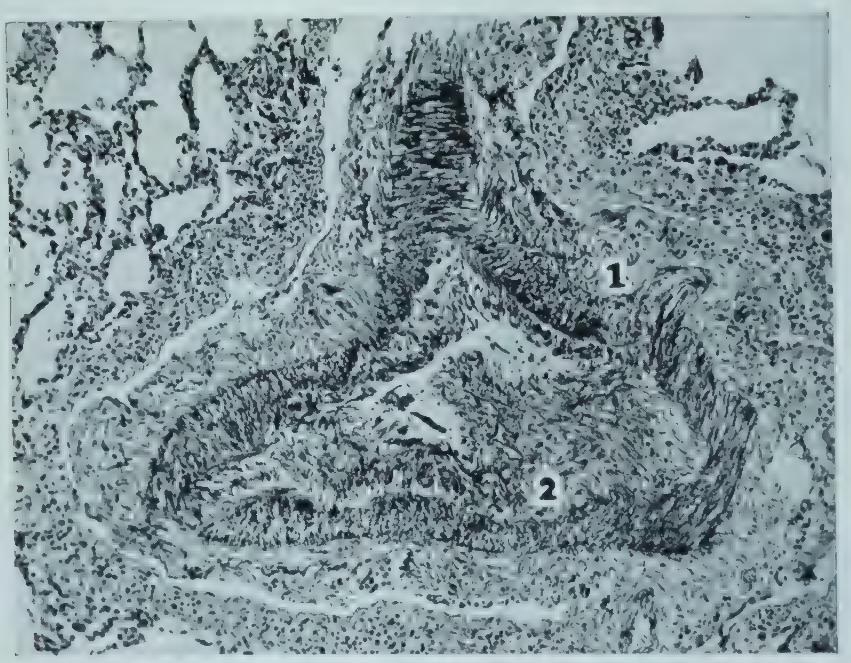

Fig. 33.—Case C. Pulmonary artery showing 1, partial necrosis of vessel wall. 2, Conspicuous intima proliferation characteristic of endarteritis obliterans.

Necropsy Studies. A summary of the histopathologic findings in the most important organs of these cases is as follows.

Pulmonary Lesions. The fugitive pulmonary infiltrations revealed by

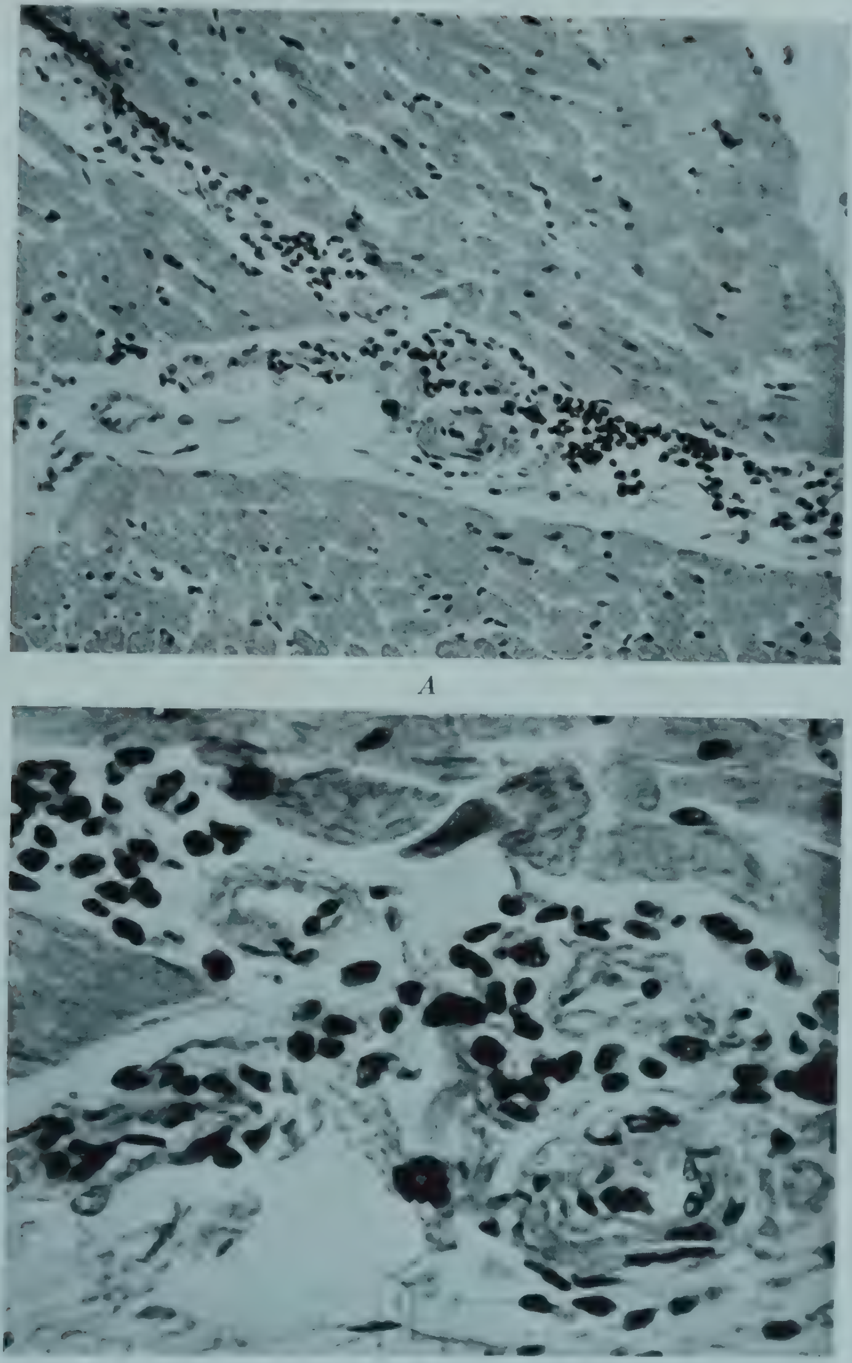

Fig. 34.—Case C. Heart muscle. *A*, Low power magnification. Eosinophilic infiltration of myocardium. *B*, High power magnification. Eosinophilia and blood vessel. (Harkavy, J. Allergy, *14*:507, 1943.)

x-ray examination were found to be due to congestion, edema and thrombi in small vessels in Case A, infiltration of the interalveolar septa with eosinophils, polynuclear and lymphocytic cells plus edema in Cases B and C (Fig. 32). The eosinophilic inflammatory involvement of the

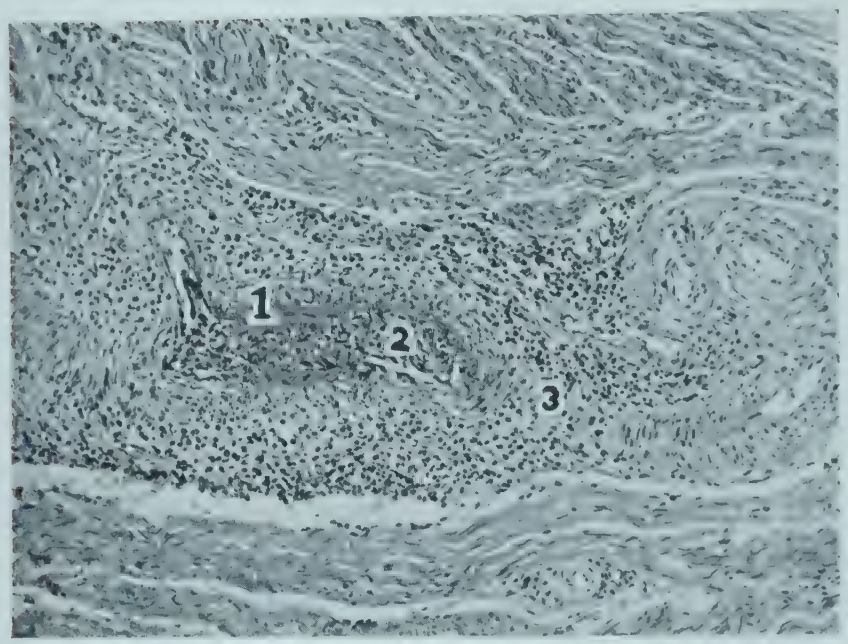

Fig. 35.—Case C. Artery of the cervix of uterus showing: 1. Necrotizing arteritis. 2. Endarteritis obliterans. 3. Periarteritis with conspicuous eosinophile cells. (Harkavy, J. Allergy, *14*:507, 1943.)

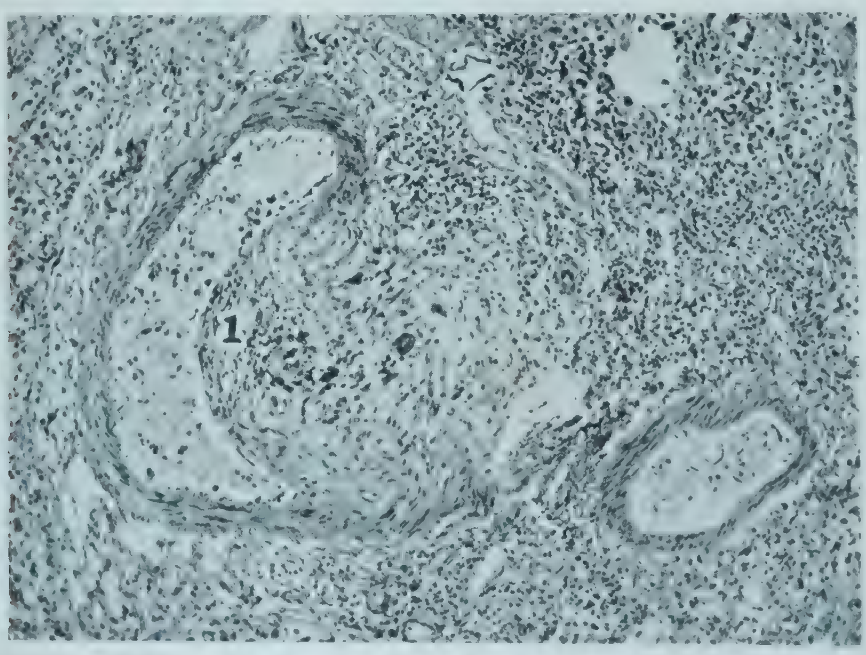

Fig. 36.—Case B. Necrotizing arteritis of a pulmonary artery surrounded by eosinophile cells. (Harkavy, J. Allergy,*14*:507, 1943.)

bronchial tubes with edema and hyalinization of the basement membrane characteristic of bronchial asthma was also seen. In addition, atelectasis and emphysema varying in extent depending on the duration of the asthma were present. In Case D the significant findings were pulmonary congestion and areas of infarction, indicative of the terminal events in the underlying vascular disease. The most important pathologic lesion in the lungs was the hyperergic reaction in the pulmonary vessels. This varied from the simple thickening of small vesssels involving the intima in Case A, to acute necrotizing arteritis with periarterial eosinophilic infiltrations in Case B (Fig. 36) and endarteritis obliterans in Case C (Figs. 33 and 35). In the pleura the hyperergic response was characterized by sclerosis of small vessels and inflammatory exudate with eosinophils.

Pericardial and Cardiac Lesions. The pericardium showed acute and chronic inflammatory alterations with eosinophilic infiltrations, sclerosis of small vessels and diffuse fibrosis.

The heart showed chronic inflammation of the endocardium and myocardium. The myocardium in Case A disclosed arteritis with perivascular fibrosis, diffuse inflammation with eosinophilic exudate superimposed on chronic granulation tissue; in Case B there were vessel changes characteristic of periarteritis nodosa, atrophy and degeneration of muscle fibers, areas of necrosis and giant cell reaction; in Case C (Fig. 34) there were areas of myofibrosis, diffuse infiltration of the cardiac muscle by *eosinophils;* and in Case D there was noted diffuse fibrosis of the myocardium and periarteriolar fibrosis. Endophlebitis and acute thrombosis of the inferior vena cava were an additional finding in this case.

Abdominal Lesions. The liver exhibited amyloidosis and vessel changes in the nature of healed periarteritis nodosa in Case A, vessel changes signifying periarteritis nodosa in Case B; and passive congestion and disseminated granulomatous areas indistinguishable from tubercles in Case C, although no tubercle bacilli were found either on section or guinea pig inoculation; and arterial thickening with fibrous replacement of the media and destruction of the elastic membrane in Case D.

The gastro-intestinal tract in Case C showed endarteritis obliterans probably responsible for the ulcerative colitis which this patient had during life. In Case D the small and large intestines were congested and the pylorus disclosed a serosa thickened and infiltrated with lymphocytes, and a recanalized vessel with perivascular fibrosis.

The kidneys in Case A presented amyloidosis, in Case B there were vessel changes indicative of periarteritis nodosa, in Case C disseminated tubercles similar to those found in the liver and spleen, and in Case D arterial fibrosis. It is significant that only in Case C did the kidneys participate actively in the clinical course, being responsible for hypertension and uremia.

The medium-sized vessels in the cervix and the uterus in Case C (Fig. 35) in addition to endarterial changes showed striking periarterial infiltration with fibrinoid necrosis of the proliferated intimal connective tissue.

General Considerations. The importance of the vascular reactions in the symptomatology of the aforementioned cases is obvious. The fact that all of the patients in this group were asthmatic implies that we are dealing with allergic individuals who by their very nature tended to respond to antigenic excitants. The existence of polyvalent sensitivity, the variations in the degree of the vascular response implicating arteries and veins, together with the characteristic presence of fibrinoid necrosis of collagen connective tissue seen in biopsy sections in some of our cases, although not limited to hyperergic reactions, fit into the concept of the pathogenesis of hypersensitiveness.

Polyvalent sensitization was evidenced in the multiplicity of the exciting agents of bacterial and non-bacterial origin which in at least seven of the cases acted synergistically in precipitating the asthma syndrome. The sinuses were the only known foci of infection, yielding a variety of bacterial flora on culture. The microorganisms recovered from the sinus washings and bronchial secretions differed not infrequently in the same individual with each new paroxysm.

The vessel changes resulting from this polyvalent sensitization, as observed in the histologic section in the various shock organs, ran the gamut from simple arterial thickening to perivascular eosinophilic infiltrations, necrotizing arteritis, periarteritis nodosa, endarteritis obliterans and fibrosis of small and medium-sized arteries. The last represented the end results of a preceding arteritis. Involvement of the veins was characterized by endophlebitis of the inferior vena cava, in one case resulting in a superimposed thrombosis. It should be noted that vessels in various states of reactivity were present not only in different tissues in the same patient, but also in the same organ. This was exemplified by findings in the cervix of the uterus in Case C, where the medium-sized arteries showed endarterial changes with marked periarterial eosinophilic infiltration as well as fibrinoid necrosis of the proliferated intimal connective tissue.

The fact that similar allergenic excitants are capable of precipitating asthma and related multiform vascular lesions in the lungs, heart and other tissues is supplemented by the reports of cases of bronchial asthma in association with periarteritis nodosa by Cohen, Kline and Young,[53] Spiegel,[54] Rackemann and Green,[55] Berger and Weitz[56] and others. These observations strengthen the concept that bronchial asthma is the symptomatic expression of an underlying vascular response and that the concomitant changes in the vessels do not represent disease entities but rather qualitative as well as quantitative degrees of hyperergic reactions.

Other clinical evidence is provided by Clark and Kaplan[46] who found in patients dying four and nineteen days after serum sickness, necrotizing arteries and periarteritis of the small coronary vessels as well as histologic changes in the mural and valvular endocardium, the aorta and pulmonary vessels. Rich[47] described lesions characteristic of periarteritis nodosa in the viscera of five patients who shortly before death had developed hypersensitive reactions following therapeutic injection of foreign serum. Four of these individuals had received sufonamides; in at least two of them there was evidence that the allergic manifestations were the result of serum sickness and not due to drug sensitization. In one patient who had received sulfathiazole as a prophylactic measure against aspiration pneumonia and in whom no infection appeared at autopsy, vessel changes indicative of periarteritis nodosa were found in addition to widespread focal inflammatory necrotic lesions previously described by Lederer and Rosenblatt.[57] That the sulfonamides as well as arsphenamine may likewise be responsible for myocarditis characterized by infiltration of mononuclear and polymorphonuclear leukocytes including eosinophils is indicated in reports of French and Weller,[58] Sikl,[59] and Brown and McNamara.[60] It is obvious that these drugs behave in a manner similar to serum sensitization.

While such inferences are based essentially on clinical and pathologic studies, they are also reinforced by the findings in experimentally induced reactions in the heart and blood vessels in rabbits following bacterial and serum sensitization. (Gruber, 1925,[61] Vaubel, 1932,[13] Junghaus, 1933,[62] Masugi and Sato, 1934,[63] Klinge,[64] Klinge and Knepper, 1935,[65] Rich and Gregory, 1942.[66]) Rich and Gregory were able to demonstrate lesions closely resembling periarteritis nodosa in rabbits sensitized by a single large dose of horse serum as well as by repeated injections. In guinea pigs sensitized with horse serum Wilcox and Andrus[67] succeeded in recording by means of direct leads from the isolated heart various electrocardiographic abnormalities usually associated with mechanical constriction of the coronary arteries, on exposure to small amounts of homologous antigen. The deviations consisted of acceleration of the heart rate and alteration in the amplitude of contraction. The PR interval was prolonged, and there were changes in the form of the QRS and T complexes, as well as ectopic rhythms. They were also able to establish that these changes were due to actual alterations in caliber of the coronary vessels and not to an increase in heart rate or muscle tonus.

In the light of the foregoing it becomes clear that *the vascular reaction represents the fundamental response to sensitization*, and the resulting clinical symptoms will depend upon the degree of antigenic stimulation, the number and kind of shock tissues involved.

Treatment. In treating patients with cardiovascular allergy it is important to establish in any given case the nature of the allergenic excitants responsible for the presenting symptoms. Sensitization to pollens, tobacco, foods or drugs is determined by the usual skin tests or elimination diets. The offending substances should be removed and immunization against pollens and other inhalants should be carried out as indicated. In instances in which bacterial allergy is suspected of playing the major role or is in association with other forms of hypersensitiveness, investigation of various foci of infection, especially the sinuses, is indicated. This is particularly pertinent in patients who present themselves with symptoms of bronchial asthma accompanied by marked eosinophilia, with or without electrocardiographic changes suggestive of an underlying vascular allergy. In such cases irrespective of a negative history of previous upper respiratory infection it is advisable to examine the sinuses, especially the antrums, tonsils and teeth for evidence of disease. The sinus washings should be cultured in order to determine the nature of the bacterial invaders as well as for the preparation of a vaccine for subsequent treatment.

The management of the infected sinuses at the outset may be conservative but if unsuccessful after a reasonable time and the patient's symptoms continue, a radical operation on the sinuses should be undertaken if the patient's condition warrants it.

Antibiotics such as penicillin may be used whenever the need arises. The use of sulfa drugs should be avoided especially in the larval form of vascular allergy because of possible additional sensitization and development of periarteritis nodosa.

The symptomatic treatment of the asthmatic seizures based on underlying involvement of the pulmonary vessels is similar to that employed in the ordinary forms of this disease. Epinephrine and intravenous aminophylline are invaluable for the control of the acute paroxysms. Autogenous vaccines in conjunction with specific therapy should be used if indicated.

If asthma and associated manifestations are uncontrollable despite various forms of therapy, removal to a dry warm climate may be helpful.

In patients in whom the vascular disease of the coronary vessels leads to cardiac insufficiency, therapy to combat the failing heart is necessary. This is carried out by the use of mercurial diuretics, oxygen inhalations, digitalis, aminophylline and venesection.

Renal insufficiency resulting from the involvement of the vessels of the kidney in the generalized hyperergic vascular response should be treated by various supportive measures. These consist of restriction of salt and protein intake. The administration of fluids should be regulated according to the nature and degree of cardiac and renal failure.

Summary

A review of the data presented here indicates that certain hypersensitive individuals whose cardiovascular system constitutes the major shock organ may under allergenic stimulation develop clinical manifestations referable to the heart and blood vessels. Reactions in the peripheral vessels including veins and arteries may give rise to the symptom complexes of migrating phlebitis, thrombo-angiitis obliterans and intermittent claudication. The altered response in the coronary vessels and myocardium is evident electrocardiographically by abnormalities in the auricular and ventricular complexes, and clinically by angina pectoris, extrasystoles, paroxysmal tachycardia and auricular fibrillation.

Similar responses may be evoked in a sensitized heart by non-specific stimuli of psychic or emotional origin. The underlying process involved here, however, is neurogenic rather than immunologic. This concept finds support in the observations of Grant, Pearson and Comeau[68] in their studies on urticaria induced by emotional stimuli. These workers offer a purely hypothetical explanation as follows: the wheal reaction is the result of impulses of central origin which pass through the efferent peripheral nerves and liberate acetylcholine, or substances closely related to acetylcholine in their pharmacologic effect. The acetylcholine thus set free as a result of stimulation of cholinergic nerve fibers leads to the release of H-substance responsible for the urticaria.

The possibility that a similar mechanism is involved in the development of certain types of angina pectoris and coronary artery disease is furthermore strengthened by the experimental production of coronary artery disease in dogs by the repeated injection of acetylcholine (Hall, Ettinger and Banting[69]).

These cardiovascular manifestations may be reversible in the early stages but later on, because of chronic inflammatory and degenerative changes which may follow repeated single or multiple antigenic stimulation, become irreversible. Reversibility and arrest of these disease processes in any intermediate stage is moreover possible, provided the offending agent is recognized and removed. This may be readily accomplished in the case of non-living sensitizing substances, as contrasted with those of bacterial origin where identification and elimination of the specific agent is infinitely more difficult and at times impossible.

In instances where the vessels of the bronchi alone are affected, asthma or cough may supervene without any demonstrable x-ray changes in the lungs. When, however, the pulmonary vessels also participate, there may develop inflammatory exudates in the pulmonary tissue which appear roentgenologically as an infiltrative process simulating pneumonia, miliary or exudative tuberculosis, associated with cough and asthma. With the extension of the vascular reaction to other organs such as the myocardium, the serous membranes, the joints, the skin or other tissues, various clinical complexes may supervene indicative of functional derangement of the involved organs, the allergic nature of which may be identified by the history or the presence of asthma and/or eosinophilia. In those cases in which the lesions are limited to the lungs, heart, pleura and pericardium there may develop a pulmonary myocardial, a pleuropulmonary-myocardial or pleuro-pulmonary myopericardial syndrome, also referred to as *mediastino-pericarditis*. Should the mediastino-pericardial reactions not completely resolve but go on to cicatrization the picture of constrictive pericarditis may supervene. This was demonstrated in several of the sixteen cases studied. The subsequent implication of all the serous membranes in the allergic response gives rise to polyserositis or Pick's syndrome. Thus constrictive pericarditis and polyserositis may be regarded as manifestations of allergic reactions involving the capillary endothelium of the serous membranes to a variety of allergenic excitants.

While marked vascular involvement may lead to irreversible changes in vital organs and a fatal issue as observed in seven of the cases under discussion, it should be emphasized that there is a large group of patients, nine in this series of sixteen, who present similar but less severe hyperergic responses in whom the pathologic process is reversible and fortunately limited to two or three organs such as the sinuses, lungs and heart. Cases presenting such symptoms may be distinguished from the more common types of bronchial asthma by the presence of a characteristically high blood eosinophilia, fugitive pulmonary infiltrations and electrocardiographic changes. These cases may be regarded as the formes frustes of diffuse allergic vascular disease. Prompt diagnosis and adequate treatment may insure the reversibility of the vascular process and forestall the extension of the disease.

Therapy must be directed towards the elimination or the neutralization of every possible allergen. Radical sinus surgery if necessary ought to be undertaken as early as possible. If this does not control the infective focus, change to a dry warm climate should be tried.

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Section VII

ALLERGY IN RELATION TO OTHER SPECIALTIES

23. *Allergy of the Digestive System*

ROBERT A. COOKE

Symptoms referable to the digestive tract are probably more common than those of any other system. They result from organic, or quite as often, from functional disorders. These latter may be regarded as reflex, toxic, psychic or allergic in origin, or due to endocrine or nutritional (vitamin) disorders. Their separation is indeed not easy, if they can be separated, for several factors may be operating at the same time. It is my intention to attempt a picture of the allergic manifestations and the criteria for a differential and etiologic diagnosis.

Definition. First it is necessary to define what should not and what may properly be included in the category of Allergy of the Digestive System and, more particularly, of the gastro-intestinal tract. Almost every asthmatic patient with continuous dyspnea or in a cycle of recurring attacks will contend that eating, sometimes certain foods, often any food at all, not only induces or increases the severity of the asthmatic attack but likewise produces abdominal distention, heartburn, eructations and flatulence. This is seen in cases of pollen asthma when no allergen other than pollen is the factor, for when the pollen has gone and the attack has abated, the foods formerly incriminated no longer produce the "indigestion." The same thing happens, perhaps more often, in patients with infective asthma. The food, which under particular conditions appears to incite the symptoms, is not really the causative allergen, for it acts only under these special conditions and as a rule the symptoms are not limited to any one food or class of foods. This is not gastro-intestinal allergy as I shall define it, but is better understood as a reflex digestive disturbance perhaps due to the irritability of the autonomic nervous system, a condition frequently associated with all allergies, especially asthma, for the intestinal tract is peculiarly susceptible to dysfunction from such causes.

Nor is it possible to include "bad breath" and "coated tongue" or the physiologic effects, perhaps exaggerated, of certain foods as onion, radish or cucumber, when patients complain that they "repeat," for these symptoms will not fall within the limits of our definition.

Since allergy is the reaction resulting from the union of antigen with sensitized cell, the term gastro-intestinal allergy should be applied only to definite sensitization reactions involving this tract. In other words there must be a lesion of the digestive tract, functional and reversible as a rule, but nevertheless a local tissue response to an allergen with symptoms referable to these organs though systemic symptoms, as urticaria or asthma, may or may not be associated.

There is no particular symptom or syndrome that is characteristic of allergy, for the varied symptoms referable to these organs and tissues, pain, vomiting, diarrhea, etc., are common to many gastro-intestinal disturbances, be they organic or functional; that is reflex, allergic, etc., and it is the duty and responsibility of the physician to evaluate them in terms of their origin and cause.

One other point to be noted is that the mistake must not be made of considering food allergy and gastro-intestinal allergy as synonymous. Ingested substances (food and drugs) cause many allergies outside the gastro-intestinal tract with or without gastro-intestinal symptoms. Allergic gastro-intestinal symptoms may arise from many causes other than ingested foods and drugs, such as infective agents and parenterally introduced biologicals.

Incidence

There are no available data on the frequency of gastro-intestinal allergy, either absolute or relative to the other functional and organic causes. Much has been written on the subject, but a critical examination discloses the fact that while allergy might properly be suspected as the cause of symptoms, in rather few instances is the proof substantial. Rowe[1] has said "all of these facts . . . make me feel that gastro-intestinal food allergy is a common and usually overlooked cause of many mild and obscure, as well as moderate and severe symptoms of this type." Feinberg[2] states, "The importance of gastro-intestinal allergy has not been fully appreciated by most allergists." Rackemann[3] believes that "allergy which is manifested solely or chiefly by gastro-intestinal symptoms is very unusual." My own experience leads me to state the frequency in this way; acute gastro-intestinal symptoms, with or without systemic evidences (urticaria, asthma), from allergic lesions reasonably assumed to exist in the tract are unusual but not rare. They occur in patients with immediate reactions following ingestion of food or drug allergens and also, though rarely, as part of the constitutional reaction from overdoses of pollen and inhalant allergens. But these are not the cases that constitute the problem of the physician as a rule, for patients themselves are aware of these immediately reacting allergens and avoid them. Cases proven to be allergic, having had persistent or recurring gastro-intestinal symptoms that constitute the primary reason for seeking medical advice, are not, in my opinion, common and certainly not as common as might be inferred from the literature on allergy. Nor are they readily solved as a result of study from a standpoint of allergy.

Immunopathology

General Anaphylaxis. In the experimental animal, lesions in the intestinal tract are observed after anaphylactic shock in the guinea pig, rabbit and dog. In guinea pigs, multiple petechial hemorrhages are often found and according to Gay and Southard[4] are more often seen in animals dying slowly. The lesions have not been studied as to their origin, but it is generally inferred that they are not primary mucosal sensitization reactions but are secondary to the blood changes, as those of the rabbit are secondary to congestive heart failure. In the dog the gastro-intestinal lesions are a prominent feature of the shock reaction (Biedl and Kraus[5]) (Schittenhelm and Weichardt[6]). Regardless of the details and intricacies of the anaphylactic reaction in the dog there is always extreme splanchnic engorgement, enlargement of the liver, a reduction of blood coagulability and a striking fall of blood pressure. Even in the dog, with its extensive hemorrhagic intestinal lesions, Manwaring[7] does not believe this condition to be primarily a local anaphylactic tissue reaction for as a result of careful experiments, he states, "that the lesion is not due to the direct action of a circulating anaphylatoxin but is due to the local action of intestinal enzymes favored by the reduced blood flow and reduced peristalsis."

Afendulis and Gülzow[8] sensitized dogs, then observed through the gastroscope the changes in the membrane after the intravenous shocking dose. They described the appearance of the mucosa as that of an acute gastritis, redness and edema with spasm, hypersecretion and hyperacidity. The reaction began to subside in two to three days. However, in view of the accepted hyperemia of the abdominal viscera in dogs in anaphylactic shock such effects may represent merely the changes resulting from passive hyperemia in the organ.

Local Anaphylaxis. Studies in local anaphylaxis have been carried out by Shapiro and Ivy[9] using sensitized rabbits and dogs. Acute gastric ulcers were produced by the local injection of antigen in the pyloric area. These were of the nature of Arthus lesions. The ulcers always healed rapidly with few exceptions, and while they appeared to become chronic (thirty-odd days) in a few instances, nothing analogous to the peptic ulcer of man was produced, though these experiments did establish the fact that local anaphylactic lesions could occur.

The experimental observations of Walzer[10, 11, 12, 13] and his associates are infinitely more enlightening. In 1937 Straus[14] reported that the skin-sensitizing antibodies which appear in the spontaneous allergies of man can be transferred to and will sensitize the skin of the Macacus rhesus monkey just as they do that of normal man. Walzer's[11] group showed that in monkeys an actively transferring human serum would specifically sensitize the mucous membrane or serous membrane of the ileum, cecum, stomach and gallbladder, but not the spleen, liver, lymph glands, striated muscle or uterus. The local reactions resembled those of the skin, and in addition there was hypersecretion and hyperperistalsis and spasm of the viscus. In this connection one point is significant, that in monkeys sensitized with potent human serum there was no evidence of sensitivity of smooth muscle although a reaction was demonstrable at the time in the skin by intradermal test.

They then proceeded to show[12] by observations on patients with mucous membrane already exposed at ileostomy and colostomy sites that a sensitization could be transferred by a sensitive human serum to the mucous membrane of normal man. The membrane reactions were analogous to those elicited in the skin—edema and hyperemia—but in the case of mucous membrane there was an increase of mucus secretion and peristalsis.

The allergies of man which are of principal concern may be best considered according to the general classification as outlined in Chapter 2, that is (1) the hereditary or spontaneously developing sensitizations, and (2) the induced, that is, acquired by accidental or purposeful contact.

(1) **Hereditary Allergies.** In the hereditary allergies the skin-sensitizing antibody is the mechanism which mediates junction of allergen and sensitized cell and produces the "*immediate*" edema-erythema (wheal) reaction. It is the only discovered basis of these allergic reactions; no smooth muscle or precipitating antibodies are demonstrable. The specific functions of the different antibodies, namely those that sensitize skin and mucous membrane in contrast to those that sensitize smooth muscle, were first brought out by Cooke and Spain.[15] This work has been amply confirmed. That the skin-sensitizing antibody exists in the mucous membrane of nose and eye is readily demonstrated in hay fever. Walzer[10, 12, 13] has shown that this same antibody will locally sensitize the mucosal cells of the hollow viscera and produce the same edema-erythema response on contact with an allergen directly applied or carried through the blood.

This same effect may properly be presumed to occur in those reactions that, on a clinical basis, are spoken of as "delayed" (see p. 27) because the allergen is a split product of protein digestion and requires time for elaboration. The mechanism of reaction is the same as in the immediate type, that is, a skin-sensitizing antibody, but there is no demonstrable smooth muscle antibody and no precipitin.

In the intestinal reactions of these types (clinically immediate and delayed) the resulting symptoms are readily attributed to the mucosal edema and hyperemia which naturally produce hyperactivity of the secretory and mucous glands and reflexly stimulate peristaltic contractions and spasm.

(2) **Induced Sensitization.** Induced or acquired sensitivity occurs in two forms: (*a*) that in which the allergic reaction is immediate—the anaphylactic, and (*b*) that in which the reaction is delayed.

(*a*) *Immediate Reaction.* In cases of the anaphylactic type of sensitization to foods, as studied by Schloss and Anderson,[16] there is antibody development analogous to that after serum disease, for patients are sensitized by the enteral absorption of protein. The blood of twenty-four of thirty-seven infants with athrepsia gave positive precipitin tests with milk, and with eight of thirteen of the positive bloods transfer of sensitization to guinea pigs was effected as evidenced by anaphylactic shock. In other words, not only precipitin but smooth muscle-sensitizing antibody was demonstrated just as after serum disease. Skin tests for the presence of the skin-sensitizing antibody to milk protein are not recorded. Of particular significance, though baffling, is the fact that in spite of the presence of these anaphylactic antibodies none of the usual symptoms of allergy, such as urticaria or asthma, was observed when milk was given by mouth, and the question remains unanswered as to whether the sensitized state was a cause of athrepsia or merely the result of the intestinal permeability occasioned by malnutrition. However, in the light of such definite findings, future studies of presumed gastro-intestinal allergy would be enhanced by the use of serologic studies and further light might be thrown upon the etiologic significance of such antibodies if they were present.

(*b*) *Delayed Allergies.* In addition to the natural and acquired sensitizations with immediate reactions which have a fairly well developed serology, there are delayed immunologic reactions to bacterial substances or products of bacterial growth portrayed by the tuberculin type reaction, by the allergic dermatitis produced by various substances such as plant phenols, dyes and metals, and by vascular degeneration due to serums and drugs. Any or all such reactions may have their counterpart in lesions of the hollow viscera just as they have in the skin and other tissues. Frankly, they have not yet been identified and described, except perhaps for ulcerative colitis and purpura with intestinal hemorrhage (Henoch's disease). They are mentioned here as a suggestion for possible future study and not as evidence of present positive knowledge.

Pathologic Physiology

The normal pattern of sensory, motor and secretory activity of the gastro-intestinal tract may be greatly disturbed as a result of acute or chronic lesions from any cause whether organic or functional. There is no pathologic physiology that is strictly characteristic of allergy.

In all acute reactions, including those due to allergy, mucous membranes become edematous and hyperemic as noted by gastroscopic examination reported in the experimental and clinical observations.[8, 17, 18, 19, 20, 21, 22] As a result of the irritation there are hypersecretion and hyperacidity, and roentgenograms indicate pylorospasm, hyperperistalsis and in the small intestine, an abnormal segmentation.

Hyperacidity. There are not many observations on gastric acidity in patients with an acute allergic gastric reaction to antigen, but there have been a number of studies on gastric secretion in allergy patients in general since Bray's[23] report that 80 per cent of 200 asthmatic children were below normal in free hydrochloric acid. As a result acid therapy was reputed to be beneficial in varying degrees by Peshkin and Fineman[24] (1930), Beckman[25] (1933), Scheer[26] (1928) and others. It enjoyed but a short vogue, for in 1936 Loveless[27] made a careful study of 138 allergic children and adults and found that the mean free acid was higher than normal in the allergic group. In a small group of three boys and two women with gastro-intestinal allergy there was a weighted free acid above that in a comparable allergic group and well above the Vanzant[28] normal. As Loveless says "gastro-intestinal allergy in this small group was associated therefore with an increase in free acid over normal and even over the allergic average."

Observations on acidity in acute gastro-intestinal allergy are not recorded and probably would be useless any way.The amount of free acid in the gastric contents or vomitus could not be accurately determined on account of the high protein content of the foods—milk, egg and shellfish—causing the reaction. The usual standards for an Ewald meal would not apply.

Hypersecretion. That there may be hypersecretion is illustrated in the case of a person allergic to horse serum whom I encountered many years ago. He had a severe shock reaction following diphtheria antitoxin. About two hours later as he was beginning to recover consciousness there was vomiting of an incredibly large amount of thin mucoid secretion, but no food, for he had had nothing to eat or drink for several hours. Apparently the stomach had partaken of the general reaction, and there was pylorospasm and hypersecretion. This is quite analogous to the mucoid hypersecretion from the ileum and colon expressing itself in diarrhea when that part of the tract is affected.

Hyperperistalsis and Spasm. There have been a number of roentgenologic studies[29, 30, 31, 32, 33, 34] in cases with gastro-intestinal allergy.

and in some instances the roentgenograms were made after the ingestion of allergenic foods. Gastric retention, increased intestinal motility with abnormal segmentation of the small bowel, and colonic spasm have been noted.

Certain of these changes are illustrated in the roentgenograms of the patient studied by Hampton and myself.[35] Patient C. Z. had hay fever (ragweed), asthma (milk and infection) and occasional intestinal disturbances with pain, nausea and diarrhea. As a result of a history of dislike for milk and three clinical trials with milk, the last under hospital supervision, it was established that, beginning two hours after taking milk, nausea, then asthma, then abdominal pain and diarrhea developed in sequence. Skin tests were positive to the primary and secondary proteoses of whey of cow's milk but were negative to milk (whey and casein) and to the proteoses of casein. The former gave a good positive immediate wheal reaction in the patient's skin, and his serum transferred the same reaction to a normal test subject. The roentgenograms taken six hours after the barium milk meal showed such significant changes as gastric retention, small intestine hypermotility and segmentation (Figs. 37 and 38). This case is an interesting example of the clinically delayed reaction, the late appearance of symptoms being due to the time required for the digestion of the milk to the proper stage (proteose) for antigen activity.

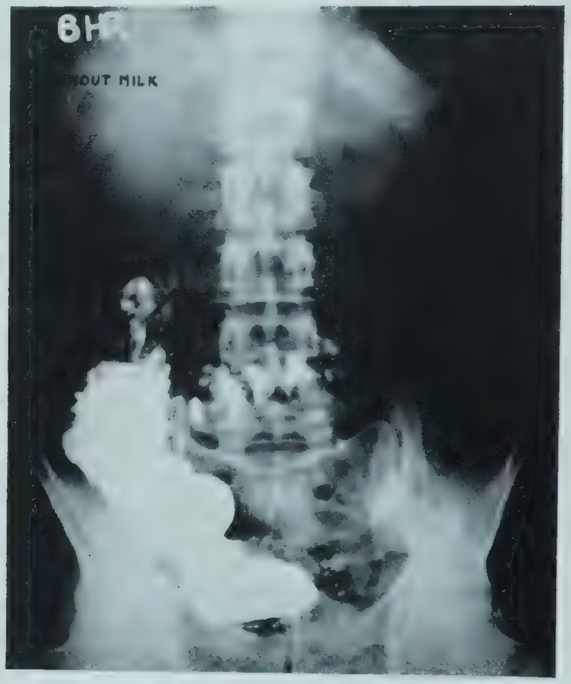

Fig. 37.—Six hours after barium without milk. Note the essentially normal movement of barium through the bowel. (Annals of Internal Medicine, Vol. 16, I, 1942.)

In a roentgenographic study particularly directed to the small intestine of allergic patients and anaphylactic guinea pigs, Wing and Smith[36] found significant variations from normal in seven of nine patients after feeding the allergen. On the contrary, thirty guinea pigs sensitized to egg were given antigen (egg mixed with barium) by introducing it into the oropharynx, and "no alteration in the small bowel pattern was noted in the sensitized pigs even when they were in fatal anaphylactic shock."

As far as roentgenographic studies are concerned, in well-founded cases of allergy of the digestive tract, there are significant changes in a large percentage, but no alteration that can be regarded as pathognomonic of an allergy. The studies throw some light on the mechanism of the production of symptoms which may result from the altered physiology resulting from an allergic reaction. I concur entirely with Wing and Smith[36] when they say in their summary. "As an aid to diagnosis, however, it [x-ray] is of limited usefulness because of the influence of nutritive foods on the behavior of the small intestine." And I must add that the technical difficulties, the time and expense preclude the use of x-ray except possibly as a confirmation in cases in which an etiologic diagnosis has already been made.

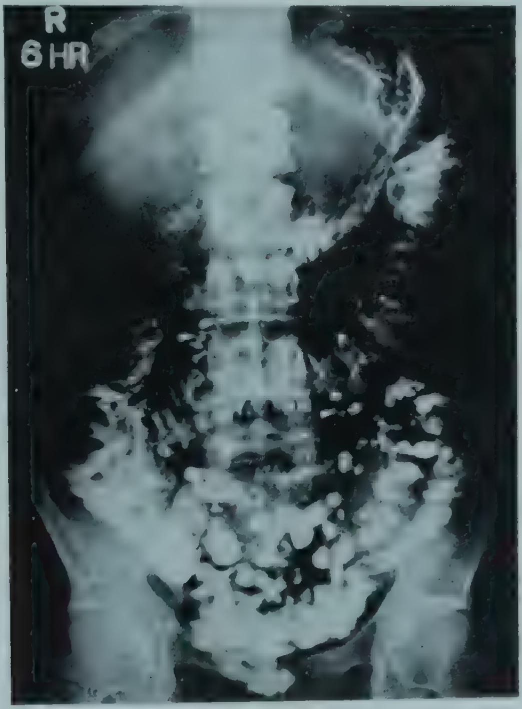

Fig. 38.—Six hours after barium and milk. Note the gastric retention, the hypermotility and segmentation in the small intestine.

Etiology

Predisposing Causes. These exist, as they do for other hereditary allergies, as shown by an antecedent or personal history of allergy, past or present.

The actual basis for any and all gastro-intestinal allergies lies in the existence of a state of cellular sensitization involving the tissues of the digestive tract, and the ensuing reaction which gives rise to symptoms must be real and of a nature analogous to other recognized allergies. This automatically rules out the symptoms of reflex, psychic and other origins as not based upon local tissue sensitization.

Specific Causes or Allergens. These include foods, drugs and biologicals, bacterial products, and possibly air-borne substances. They reach the sensitized tissues directly by ingestion or after absorption through the blood or lymph.

Foods. These are by all odds the most common allergens. The important ones are milk, egg white, egg yolk, chocolate, fish, shellfish, nuts, cottonseed, celery, peas, corn, sweet potato, pork and chicken, buckwheat and honey. It must be emphasized that any food may be a cause in some particular case. I have seen several severe reactions from beer (hops), and one each from artichoke and mushroom. I take exception to the importance of wheat and cereals as frequent causes, even in those who have positive wheal reactions. Bakers and cooks who have asthma and coryza from inhaled wheat usually can eat cereals with impunity for they are ingested in well cooked form and are well aged and processed before consumption, thus destroying antigenic activity. Eyermann[31] has recorded a well substantiated case but in this instance the skin test was only equivocally positive; the reaction occurred solely with whole wheat, and symptoms did not begin until one hour after whole wheat was taken. I do not recall a case with gastro-intestinal symptoms in which cereal sensitivity was proven to my satisfaction.

Drugs. Aspirin, quinine, cod liver oil, thiamine, iodides, arsenic, mercury, the sulfonamides and barbiturates, together with such biologicals as liver and pollen extracts, are perhaps the most common offenders. It is noteworthy that with these drugs usually there are concomitant cutaneous edemas or urticaria. As with foods, many odd drugs may be allergens in any particular case.

Bacterial Products. Infection, either acute or chronic, plays an important role as an etiologic agent in the production of abdominal symptoms, generally in association with cutaneous edema. If one excludes the acute immediate allergies to foods which rarely require medical attention, bacterial products are as important as all other agents together in the production of gastro-intestinal allergies. The reaction is always of the delayed type. Any and all of the common pathogenic bacteria (and viruses?) have been implicated, especially when they are the causes of infected foci.

This is illustrated in the case of patient P. who for several years had attacks of angioedema and with many of those symptoms of nausea, flatulence, abdominal discomfort and heartburn. With the more acute cutaneous edemas the gastric symptoms were more indicative of peptic ulcer. His general condition was poor, and his hemoglobin was 60 per cent. Physical examination showed a suppurative sinusitis on the left side, secondary to dental infection. Roentgenograms of the stomach showed evidence of distortion of the cap, indicative of irritability or spasm, but there was no fixed lesion (ulcer). The free hydrochloric acid of the stomach contents was slightly elevated. Removal of infected teeth, antral irrigation, and eventually a Caldwell-Luc operation, were followed in the course of a few weeks by marked improvement in the cutaneous and gastric symptoms. No food allergies were discoverable either by skin test or dietary procedures. Improvement in his general physical condition and the disappearance of anemia were equally striking.

It is not possible in this case, as in most of the cases of allergy with gastric symptoms, to prove the existence of an allergic lesion involving the mucous membrane of the stomach. The course of events, however, indicates that the infection was the essential cause of his symptoms, either directly or indirectly, and the simultaneous appearance and disappearance of gastric and cutaneous symptoms certainly suggest the oneness of their etiology and immunology (bacterial allergy).

Air-borne Substances. Agents absorbed by inhalation are unimportant except as they may produce irritation of the pharynx or roof of the mouth, as may be the case with pollen in hay fever (see list of inhalant allergens, Chapters 10 and 27).

Symptomatology

Allergic lesions of the digestive system, whether localized or general, create symptoms dependent upon the area involved and the type and acuity of the allergy, and these symptoms duplicate in all essential respects those resulting from other functional or organic lesions of non-allergic origin.

In the mouth, edema of the tongue, buccal mucous membrane, soft palate and pharynx, and often of the larynx, is seen in conjunction with cutaneous urticaria or angioedema, or occasionally without any skin lesions. The attacks are usually mild and constitute an annoyance, but may be serious if the pharynx and larynx are involved. They last from one to several days, and as a rule are not materially benefited by epinephrine injections. An hereditary angioedema with fatal laryngeal obstruction in three generations has been reported by Osler.[37]

Stomatitis, a counterpart of dermatitis, is seen from contact with mercurial antiseptics and with the nickel of dentures, usually in those having a skin allergy to these metals. In those allergic to iodine not only the buccal mucous membrane reacts but the salivary glands, especially the parotids, become swollen and tender. and large amounts of saliva are secreted. Occasionally, stomatitis is due to a food, especially nuts and particularly walnuts. In addition to the general inflammation, tiny canker sores appear under the tongue or inside the lips and cheeks. This latter reaction is also to be regarded as analogous to dermatitis. I once reproduced this lesion by the local application of an ether-soluble substance from walnut. It behaved like a poison ivy dermatitis.

In the esophagus, angioedema may occur usually in conjunction with visible edema or in patients with a past history of edema. The symptom is usually dysphagia, or there may be a deep thoracic or substernal discomfort rather than pain. The obstruction is not complete and is temporary, a matter of a few hours, or a day at the most. Spasm of the esophagus and angina pectoris have to be considered and differentiated in these rare cases. An esophageal diverticulum is usually ruled out by a characteristic story and roentgenograms after barium.

Allergy of the Gastro-intestinal Tract. Symptoms referable to the stomach, small and large intestine may be best presented if dealt with under such general headings as dyspepsia or indigestion, peptic ulcer, acute gastro-enteritis, recurrent vomiting, chronic diarrhea, and the acute abdominal crises.

(*1*) *Dyspepsia or Indigestion.* It is noteworthy that in the recent textbooks on medicine these terms are not used, yet for present purposes they are useful to indicate a general group of symptoms including heartburn, eructation, flatulence, anorexia, nausea, and such objective findings as hyperacidity, hyperperistalsis, spasm and hypersecretion. All of these symptoms and signs are the result of sensory, motor or secretory dysfunction. In the majority of these cases symptoms are due to organic or functional non-allergic disease of the stomach and intestines, but there are some cases that are definitely based on allergy, and in chronic persistent or recurring symptoms allergy should be considered as a possible cause. In patients with definite asthma, hay fever and urticaria, the co-existence of an allergy involving the gastro-intestinal tract is a possibility in view of the known sensitization of the mucosa. In patients with similar symptoms but no other allergy, one may presume a possible allergy subject to strict diagnostic criteria, but it is in this group that skepticism must be exercised unless or until the evidence for allergy is overwhelming.

Patients with these "dyspeptic" symptoms divide themselves into two groups. First, there are those who know that a special or particular food will always cause symptoms promptly, within an hour. When tested intradermally the reaction quite uniformly is an immediate wheal. It is because of the immediateness of the symptoms that patients have made their own diagnoses and abstain from the reacting food. Another point about these cases is the fact that the reaction is often limited to a single article or possibly a few that are closely related, for example it may be egg alone or egg with chicken and chicken broth. Such patients do not seek medical advice for their abdominal allergy.

With the second group the symptoms are not so closely related to eating and therefore are not readily identified by the patient. In illustration I may cite the case of a woman twenty-five years of age who, in addition to persistent but mild urticaria, had heartburn, sour eructation, fullness and loss of appetite for six months. All skin tests including those with fish were negative. First, a food diary was suggested with specific data on all foods eaten and the existence and degree of symptoms. By restricting certain types of foods it was eventually determined that fish, usually eaten twice a week, was the factor, for by use and avoidance of fish both urticaria and indigestion could be regularly produced and stopped, but symptoms did not begin for eighteen hours after ingestion and lasted about three days. Also in this case there was a certain but limited threshold of tolerance. Such a case represents the type of "delayed" clinical allergy not susceptible of diagnosis by the immediate skin test with an extract of the fish protein in the form in which it was eaten.

Another type of reaction in the delayed group (tuberculin type) is seen in patients with chronic allergies (asthma or angioedema) secondary to focal infection with associated digestive symptoms as in Case P, with chronic angioedema (see p. 401). This is a frequent syndrome. I can recall no patient with an associated allergy of asthma in whom there was substantial proof that the digestive symptoms were not a functional reflex or a sort of fatigue neurosis, but in cases of urticaria and angioedema of infective origin there is more reason to think, though still no proof, that edemas of the gastro-intestinal tract might be responsible for these so-called indigestion symptoms. However, in none of my patients have symptoms been reproduced at will by an autogenous vaccine, and this is the crucial test.

(2) *Peptic Ulcer.* Many workers[6, 8, 9] have attempted to produce peptic ulcer in the experimental animal. In spite of this work, especially that of Shapiro and Ivy[9] in the production of an Arthus type of ulcer in the stomach, there is little reason to believe that the peptic ulcer of man is of true allergic origin. That the symptoms may be aggravated by the use of allergenic foods, especially if the sensitization is to milk or egg so frequently used in ulcer diets, is indicated in the study of Kern and Stewart.[38] They observed a series of thirty-two patients with operative or x-ray evidence of ulcer. Forty per cent had a personal allergy and in 28 per cent there was antecedent allergy. Certainly these figures are well above the average for the general population. They say "of nine patients who seemed to show a relation between the eating of specific foods and the occurrence of abdominal symptoms, three also gave a history of personal allergy, had positive skin tests, were relieved

of symptoms on a nonreactor diet, and suffered a recurrence or aggravation of symptoms when on a reactor diet." These authors believe, however, that allergy is an etiologic factor "in an appreciable minority and not just in a rare or occasional instance." They call attention to its possible significance especially in cases of recurring ulcer. This is a sound and conservative statement.

Ehrenfeld et al.[39] also studied the question of allergy as a factor in the pathogenesis of ulcer. Seventy-five patients with ulcer and a control group of seventy-two allergic patients were observed to determine the presence of ulcer. In their allergic group, thirty-five or 49 per cent had definite gastro-intestinal complaints, and of this thirty-five, nineteen had symptoms of the ulcer syndrome. Only twelve had abnormal roentgenograms, four or 5.5 per cent typical of ulcer and eight with gastric or duodenal spasm. In the seventy-five ulcer patients, thirty-two knew of one or more foods that always distressed them. Nine had positive skin tests but in only three cases did the history and test agree. Since the incidence of ulcer in the allergy group is within that for the general population, the authors conclude that there is "no valid reason to assume that allergy plays an important part as an etiologic factor in peptic ulcer cases." These patients were not subjected to a dietetic study, and it is very possible that some of the thirty-five with abdominal complaints, especially the twelve with roentgenogram deviations from normal, may have had gastro-intestinal allergy the symptoms of which, as in ulcer, may be pain one to four hours after eating which is relieved by food and alkaline therapy.

The general opinion on this question of allergy as a basis for ulcer may be summed up thus. There is no proof that a peptic ulcer can be the direct result of an allergic reaction. It is conceivable that a protracted allergy in the stomach might cause hyperacidity which in its turn is responsible for the lesion but this is purely hypothetical. It must be granted that the ingestion of a food which causes an allergic gastric response would augment the symptoms of an existing ulcer, and patients, especially those with recurring ulcer, might be studied for evidences of gastro-intestinal allergy particularly if they have evidences of the allergic constitution.

(3) *Acute Gastro-enteritis.* The prompt onset of nausea, vomiting, epigastric pain and subsequent diarrhea following the ingestion of some article of food is an indication of an allergy of the immediate type and is quite uniformly confirmed by the immediate wheal skin test. Usually there is also burning, itching, and edema of the lips, tongue and throat as well as edema of the face, and general urticaria. There may be an asthmatic attack as well. The severity of visceral symptoms depends on the amount swallowed or the promptness with which it is vomited. Immunologically these cases are identical with those having simple

indigestion, only the reaction is more acute and general. There is no need to question the allergic nature of these cases. The immediateness of the reaction is the characteristic feature.

However, there are cases with symptoms that are just as acute but which do not follow promptly the ingestion of food; there is a delay of perhaps four to twenty-four hours. The patient is not apt to make an etiologic diagnosis under these conditions, and the skin test with foods is quite regularly negative. If attacks are infrequent they may be traced to some food or drug occasionally taken, but if the cause is one of the commoner foods and the patient has a reasonable threshold of tolerance to it, a diagnosis is made only by the clinical procedure of trial and error with controlled diets. In this group are those patients sensitive (dermatitis) to mercury or oil of wintergreen who unwittingly take the drug, and following the usual cathartic effect later develop severe and protracted enterocolitis; also those patients sensitive to pollens who have had intestinal symptoms after oral therapy. A cutaneous dermatitis may follow in any of these cases.

(4) *Recurrent Vomiting.* This syndrome seen in infants and children is also frequently termed acidosis, acetonemia, cyclic or periodic vomiting. Fries and Jennings[40] recently reviewed the subject and studied a small group of patients. These authors emphasize the frequent occurrence of this symptom complex in allergic children but recognize the difficulty of establishing proof in cases suspected of food sensitization. I believe that children actually or potentially allergic should be studied as cases of possible sensitization to foods or to infection. Children and especially infants, not finicky as to foods generally, who refuse certain articles in their regime should not be forced or coaxed. Sometimes the vomiting attacks are ushered in with fever and evidences of infection and appear to bear the same relation to infection as does asthmatic bronchitis. In other words the attack might be considered as a form of bacterial allergy.

(5) *Diarrhea.* Under this heading I mean to include those cases in which diarrhea, either paroxysmal or chronic, is the presenting symptom. More specifically the lesion, if it be an allergy, may be of the small intestine or more probably of the colon, and in medical nomenclature is spoken of as colitis, mucous colitis or non-specific ulcerative colitis. In addition to the frequent or loose stool there may be occasional colicky pains but more generally abdominal discomfort and a sense of soreness. These cases in which a diagnosis of allergy is permissible are usually those with other allergies which are not necessarily due to the same allergen as that provoking the diarrhea. Foods, especially milk and egg, or infection may be the causes.

Hampton[41] has cited cases of Henoch's purpura with diarrhea which were carefully studied and the food allergen determined. He found blood in the stools and eosinophils in the mucus.

In cases of infective allergy, with symptoms of mucous colitis, a removal of the focus not infrequently will clear up the diarrhea, but proof of an allergic lesion in the colon has not yet been obtained.

(6) *Acute Abdominal Crises.* By this term I mean to designate those cases in patients with very acute pain, distention, general abdominal tenderness and vomiting. In general this syndrome has been considered as probably due to angioedema of the bowel causing severe symptoms and suggestive of volvulus, mesenteric thrombosis, intussusception, perforative peritonitis, gallstone colic, or any of the acute conditions requiring surgery. Many of these patients sooner or later are operated upon. Occasionally a localized edema of the gut has been found by the surgeon, as reported by Osler,[37] but often no lesion is discovered.

These cases call for a careful diagnostic study. A clue to the diagnosis is afforded if there is a history of allergy, especially urticaria and angioedema, or if there has been an irregular recurrence of similar attacks over a period of years. The leukocyte count, temperature and abdominal signs are not dependable indices. One should seek for any extra-abdominal symptoms which would not be found in strictly surgical conditions, such as salivation, headache and pain in the arms and legs. These were found in the first of the two following cases which are probably the most striking examples of the acute abdominal crises that I have met with in my entire career. I shall quote from my earlier report[42] as it was then recorded.

> "The first case was reported by Janeway and Mosenthal in 1908 to the Association of American Physicians under the title, 'An Unusual Paroxysmal Syndrome, Probably Allied to Recurrent Vomiting, with a Study of the N Metabolism,' and was published in the Transactions of that year (p. 504). The diagnosis at that time was toxemia of endogenous origin. The essence of the history there recorded was as follows: A Jewish schoolgirl aged sixteen years suffered with recurring attacks which began, according to the mother, when she was two weeks old. In early life the frequency was once a month and the longest period of freedom up to sixteen years was ten weeks. For a year attacks had come weekly and for three months every Friday with absolute periodicity. The attack was described by these authors as having a prodromal period of uneasiness, anorexia and epigastric or abdominal discomfort lasting from four to fourteen hours. Some very mild attacks did not go beyond this stage. Next there was a crescendo period with rapid increase of symptoms, prostration, anorexia, abdominal colic, and also pain referred to shoulders, hips or feet. There was fever, tachycardia and polynuclear leucocytosis. Maximum temperature 104°; pulse, 140; leukocytes, 28,800. The only differential count recorded when leukocytes were 8,000 showed a normal eosinophile count. Occasionally there was headache. The abdomen was rigid, with tenderness at times as extreme as in general peritonitis but varying in the location of maximum sensitiveness, which was usually to one side or the other of the umbilicus. Marked salivation was noted and in severe attacks there was constant nausea and belching and occasional vomiting, the vomitus containing free HCl. This stage lasted from eight to sixteen hours and was followed by the period of recovery with rapid subsidence of pain, then fever and leucocytosis within seventeen hours. She then felt well, had a voracious appetite and within a few days regained the four or five pounds lost in the attack. Gastric analysis showed slight hyperchlorhydria.
>
> "This case was referred to me in 1916 by Dr. Halpert of Scranton who had originally

> referred her to Dr. Janeway. The subsequent history was that under later observation by Janeway at Johns Hopkins Hospital an exploratory operation had been done and the appendix removed. It was without effect. The severe attacks continued on the average of twice a month but the milder attacks were more frequent. In spite of this her nutrition remained good. Viewing this case at that time (1916) as a possible manifestation of allergy, the intradermal skin tests were done with such ordinary foodstuffs as milk, eggs, cereals, meats and the important vegetables and fruits. All tests were negative. The family history for allergy was negative. However with the hypothesis that this might be allergy and probably an allergy to food, it was a logical conception to exclude at first those foods most commonly taken by a person from infancy to the age of twenty-four, hence milk, eggs, and meats were eliminated. The attacks stopped. Milk was subsequently added to the diet on two separate occasions and the well recognized prodromal symptoms appeared at the end of two or three days. After these two experiences the patient could not again be induced to take milk. Under observation for nine years, when last seen in 1925 she had been entirely free of all attacks. She never touched milk and was not then willing to repeat the experiment. Her two children showed no allergy up to that time. The sudden cessation of attacks of twenty-four years' duration following the withdrawal of milk, and the reproduction of mild attacks on two occasions by the use of milk, together with the absence of discoverable organic lesion, seem to warrant the diagnosis of an allergy.
>
> "The second case presents even more acute evidences of a possible surgical condition. Mrs. C. B., now sixty-four years old, has no antecedent history of allergy. Her daughter has a condition similar to the one about to be described, but much milder. At about twenty-five years of age she realized that fatty fish gave indigestion with fullness and belching. At the age of forty she began to have frequent severe abdominal attacks which she herself traced to the use of pork fat. Small amounts of lean pork may be eaten without trouble. Fats other than lard in quantity will give headache and dizziness. A typical attack from lard is described as follows: About two to three hours after the fat is eaten the attack begins with abdominal distress which progresses rapidly to pain so severe that she passes into shock. The vomiting is continuous and explosive; pulse rapid; skin pale, cold and clammy. Distention of the abdomen is extreme. Formerly the attack lasted twelve hours. Due to greater care, or loss of sensitivity, the recent attacks have been infrequent and mild. There is no fever. Blood counts have not been made. Tests with lard by the patch and scratch methods show no evidence of skin sensitiveness. Two years ago this patient had a gallstone attack. There was sudden colicky pain for about half an hour every two to three hours. The entire attack lasted twelve hours and was finally relieved by morphine and atropin. The temperature was 101°. There was rigidity of the right upper quadrant and the gallbladder was palpable for several days. Jaundice was not deep but the stools were clay colored. The extreme distention, vomiting and collapse symptoms were absent. The patient states that there was a marked difference between this illness and the attacks due to lard."

These two cases represent what we are wont to regard as abdominal angioedema. In my experience they are rare. Neither of these patients had cutaneous edemas or other allergies. That their symptoms were due to a temporary reversible and therefore functional obstruction is evidenced by the prompt and complete recovery without surgical interference.

Abdominal pain of lesser degree but sufficient to demand the patient's attention is occasionally seen as the presenting symptom, sometimes with mild nausea or diarrhea but more frequently with constipation. In patients with associated allergies and a history of such atttacks over a period of considerable time the possibility of allergy probably of the angioedema type is to be considered. If the patient is seen in a first attack there is natural concern and one might better err on the side of surgical intervention than take an unfortunate chance. The adults who are "old timers" with such attacks recognize them for what they are, though they do not know the cause. One characteristic of these recurrences is that the location of the pain shifts from attack to attack and there is no abdominal rigidity or local tenderness.

In young children there is a condition of *retroperitoneal adenitis* that is very confusing. There is apt to be fever, rarely leukocytosis, the pain is not too strikingly localized but tenderness with rigidity may be present possibly in the right lower quadrant. Often such cases are operated upon and a normal appendix removed. Usually there are infrequent recurrences. Abdominal adenitis is secondary to an infection primary in the upper respiratory tract and especially in children with chronic lymphoid infection in the tonsils and pharynx. Whether this is a bacterial allergy is not proven but I believe it may be, for vaccine injections have given rise to a symptomatic reaction with abdominal pain.

Diagnosis

The only cases properly classed as allergy of the digestive tract are those in which there is a lesion brought about by an antigen-antibody-cell reaction involving some portion of the tract. I agree entirely with Eusterman (quoted by Prickman[43]) that "nervous factors are responsible for the symptoms in many suspected cases of abdominal allergy," and I believe this holds true in many of those with, as well as without, other definite allergies, though there may be more reason to give credence to allergy in the former than in the latter.

Criteria for Diagnosis. It should be possible to formulate satisfactory criteria that would help to eliminate faulty diagnosis. In 1921[44] I formulated certain postulates that should be fulfilled in establishing any substance as an antigen etiologically responsible for the symptoms under study. They were in substance as follows:

(1) Sensitization must be demonstrated either by (*a*) the immediate local wheal reaction to skin test, or (*b*) the artificial reproduction of the allergic symptom at will on proper contact with the assumed antigen, not once but preferably three times, and all conditions as to amount of antigen and the time of appearance after ingestion of allergen must remain equal on all trials.

(2) It must then be shown that the patient has been in contact with this substance in such a way and at such times as to permit it to act as the cause of the symptoms.

Before an etiologic diagnosis in gastro-intestinal allergy can be claimed to be proven, postulate (1*b*) is required. The local skin test wheal mentioned in postulate (1*a*) is relatively unimportant for when positive it often does not indicate clinical sensitiveness, as is well shown by Ehrenfeld,[39] and if negative that food may still be an allergen giving rise to a delayed reaction for many of the intestinal allergies are of this immunologic type.

Postulate (2) is of course essential, and if the ingestion of the suspected food does not regularly precede the attack at some constant interval either there is another responsible allergen or the observations are faulty.

Factors in the Diagnosis of Allergy. The first step is not to assume that the gastro-intestinal condition is allergy, for it frequently is not, but to carry out all procedures necessary for a correct diagnosis as indicated by the symptoms and signs. If these do not afford adequate information for an etiologic diagnosis then one may proceed with a study on the basis of a possible allergy.

History. The presence of familial and past or present personal allergy adds to the presumptive evidence for allergy, subject to later proof. In the personal history one striking peculiarity of clinical allergy may be the frequent repetition of attacks or their distressing chronicity. The diet and the use of tobacco, alcohol and drugs are recorded as well as the activity of the bowel (see History, Chapter 2).

Skin Tests. The skin tests for immediate wheal reactions may give a clue to the antigen, but if they are positive then the resulting symptoms must be prompt. It is inconceivable that egg white giving an immediate skin test could, when eaten, give anything other than a prompt clinical reaction. However, skin tests are often negative with proven antigens but if so, as I have stated before, the clinical symptoms do not appear for at least one hour, usually more, and may be delayed for twenty-four to forty-eight hours. In allergies of the digestive tract positive skin tests are unreliable as diagnostic aids except as confirmatory evidence of the immediate reaction of the edema type of which the patient is himself aware. To this there are only rare exceptions. If the lesion is of such a nature that a dermatitis-inducing allergen is responsible, patch tests may be used to determine the cause. However, the skin might not respond if there is a localized area of sensitization as I once found in a case of nickel stomatitis.

Physical Examination is necessary to the important differential diagnosis which must always be made, for it reveals little of a positive nature in allergic reactions. A careful study for foci of infection must be made.

Laboratory Examinations. A blood eosinophilia is rarely found except in conjunction with other allergies which are probably responsible. Eosinophilia in the mucus of the stool might be significant in cases of so-called mucous colitis and was reported by Hampton[41] in a case of Henoch's purpura.

The value of the leukopenic index originally applied to the study of food allergies by Vaughan[45, 46] is not supported by the statistical evidence in the studies by Loveless[47] and by Brown.[48] It is unfortunate that many studies on gastro-intestinal allergy such as those of L. P. Gay[49] and others[50] were based upon compatibility or incompatibility of food as determined by this index which has been proven to be incorrect and has fallen into disuse.

Roentgenologic Examination of the intestinal tract in suspected allergy is an aid that is subject to many pitfalls. A number of such studies[29, 30, 31, 32, 33, 34] have been made. The method involves a comparative study after a barium meal with and without the food allergen. The evidences that have been noted are gastric retention, increased motility, abnormal segmentation of the small intestine and colonic spasm. However, none of these findings is pathognomonic of allergy; they are merely evidences of motor dysfunction due to any cause. Moderate variations within the normal pattern are frequent. Wing and Smith[36] concluded that "as an aid to diagnosis it [x-ray examination] is of limited usefulness" and with this I agree.

Restrictive Diets. These must be used with care and for a limited period. Too many patients are at large on diets reduced below normal for adequate nutrition on the basis of unconfirmed and equivocal skin tests or on a restricted diet that was intended merely as a trial.

The clinical method of trial and error is perhaps the most useful, but it is difficult, time-consuming, and often fails. One may resort to the elimination diets of Rowe.[51, 52] My own preference is to have the patient keep a careful diary of the approximate amounts and of the ingredients of every food, drink, or drug, noting on the diary the times when symptoms are present. Foods should be withdrawn by classes or groups. First, omit all alcohol, tobacco, condiments and spices, tea, coffee and all drugs. One may then eliminate all animal protein for a week; next all fruits and vegetables utilizing Diets I and II as in the study of allergic dermatitis (p. 258). If results are obtained on either of these diets one then adds in turn certain of the more important articles that were withdrawn. The results are often disappointing unless some clue is afforded by a careful history and a study of the preliminary diet record. However, if symptoms do return one must then verify the observation by use and avoidance of a suspected food and the results must agree preferably on three trials before proof is definite.

Treatment

Symptomatic therapy is always indicated. If allergy is suspected, a subcutaneous injection of epinephrine hydrochloride (1:1000) 0.2 to 0.5 ml. may be tried. It is reported to have given prompt relief in some cases, but in my hands it has been very ineffective. If the pain is very severe codeine or some opium derivative may be used only after a nonsurgical diagnosis is assured.

The management of those cases in which a diagnosis of allergy is established consists merely in the avoidance of the food or drug that may be a determined cause. There are patients genuinely sensitive to important foods as milk and eggs, but this is rare in adults though there are such occasional cases as one reported by Sternberg[53] allergic to milk and a still more rare instance such as Eyermann's[31] wheat case. But most of these patients have a reasonable or absolute degree of tolerance to the food if eaten in well cooked form. For the exceptional case in which milk, egg or fish must be scrupulously avoided, suggestions for proper substitutes are usually easy to make on a common sense basis. My personal opinion is that this matter of allergy diets is a much overrated fad. If a patient needs more specific information on the subject it may be obtained from special books devoted to allergy diets.[51, 52, 54]

For all sensitizations other than milk, egg or wheat, avoidance is a relatively simple matter once the patient is convinced of his intolerance.

Treatment by injection of antigen is rarely if ever required. In infants most food sensitizations spontaneously disappear. There is no proof that injections or the oral drop by drop increases have ever been responsible for an increased tolerance.

If bacterial allergy is a cause the removal of a focus, immunization by vaccine therapy (see p. 151) or antibiotic treatment of acute infection is indicated.

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24. *Allergy of the Eye*

ROBERT A. COOKE

THE factor of sensitization in explanation of certain lesions involving the eye has received thoughtful study and has contributed largely to recent advances in ophthalmology. However, in the literature on allergy as applied to clinical diseases of the eye adequate account is not always taken of the different types of sensitization, namely (1) the artificially induced anaphylactic type; (2) the spontaneously occurring immediate wheal type; (3) the dermatitis reaction; and (4) the bacterial sensitizations. These have been discussed in Chapter 2.

(1) Induced Allergy. Evidence that the ocular tissues partake in the general sensitization induced by horse serum was first demonstrated by Nicolle and Abt (1908)[1] and since then has been amply confirmed. The more significant of these studies[2] on experimental animals in artificially induced protein sensitivity of the eye (anaphylaxis) concern themselves with the local immunologic response. After the injection of heterologous red blood corpuscles into the anterior chamber of a dog's eye the specific antibodies always appeared first and more abundantly in the blood and later to a lesser degree in the aqueous humor of the injected eye. This and similar studies were later repeated by Seegal, Seegal and Khorazo[3] who showed: (1) that after undiluted egg white was injected into the anterior chamber traces could be recovered from that area for as long as eight days, but none was ever detectable in the blood serum; (2) that precipitins appear first in the blood serum after an anterior chamber injection of egg white as Hektoen[2] found. Precipitins may or may not appear in the aqueous humor of the injected eye. They were never found in the anterior chamber fluid of the uninjected eye. (3) The immunologic response to a single anterior chamber injection is comparable not to a single dose but to repeated injections of diluted egg white by vein or skin route. (4) Passive sensitization of the eye by anterior chamber injections of antiserum is rarely accomplished. (5) When sufficient time (more than eight days) is allowed to elapse after antigen injection into the eye, then an intravenous shocking dose produces ocular inflammation during which time antigen may be detected in the anterior chamber fluid. This the authors believe may explain the continuation of the hypersensitive state of the eye. A further study by Seegal and Seegal[4] showed that during a local non-specific inflammation created by the introduction of glycerine into the anterior chamber of the eye the parenteral injection of the antigen will sensitize the traumatized eye quite as well as though antigen is locally introduced. This is evidenced by the ocular inflammation when the antigen is given as a reacting dose nine to twenty-six days later. If general sensitization is of sufficiently high degree both eyes may be equally affected by the parenteral shocking dose.

While the significance of these carefully executed and controlled experiments cannot yet be fully appraised it is obvious that the antigen, slowly absorbed into the body from the anterior chamber, stimulates the formation of antibodies, supposedly by the reticuloendothelial system, for there is no cellular tissue around the anterior chamber capable of creating antibody. However, when the antibody reaches a sufficient titre in the blood stream it is reabsorbed first into the eye which was slightly inflamed by the antigen injection. This is similar to the irritation produced by the glycerine injection. But the aqueous humor of the fellow eye will also absorb antibody when the antibody titre is high in the blood stream as the result of simple osmosis. Various cells in the eye then become sensitized by antibody although they cannot produce it. At this time antigen absorbed into the eye from any route produces an ophthalmic reaction.

(2) **Spontaneous Sensitization.** Quite similar to the anaphylactic type of induced sensitivity is the spontaneous sensitization so well exemplified by pollen hay fever. The immunologic mechanism of this reaction of the conjunctiva, in part at least, is identical with the induced sensitivity in that both carry the skin and mucosal sensitizing antibodies productive of the reaction. Sensitization may be determined by the intradermal skin test or by ophthalmic tests. The reaction is of the immediate wheal type, that is edema and hyperemia.

(3) **Dermatitis Reactions.** Exemplifying a still different allergic mechanism are those reactions of the conjunctiva identical with allergic dermatitis, either of the extrinsic or the intrinsic type, and which are clinically observed in cases of conjunctivitis often associated with dermatitis. This type is well illustrated by cases of conjunctivitis resulting from the application of atropine, pontocaine or paraphenylenediamine. (See Chapter 14, Allergic Dermatitis.) The reaction is a delayed inflammatory one of the dermal or epidermal layer with degeneration and exfoliation of the epidermal cells and exudation of serum. Sensitization is determined by the patch type of skin test and is not evident for twenty-four to forty-eight hours.

(4) **Bacterial Sensitizations.** Although the immunologic mechanism is probably not the same, studies have shown that bacterial infection may exert a sensitizing effect on certain tissues of the eye which thereafter react allergically to products of the specific infecting organism. The ophthalmic reaction to tuberculin (Calmette) is an example of

allergy of the eye entirely analogous to a positive Mantoux skin test. Except for certain bacteria, as the tubercle bacillus, skin tests for bacterial allergy are in general very unsatisfactory.

Unquestionably there must be caution in the too general application of the data from experimental anaphylaxis to clinical disease, and always the attempt must be made to correlate more carefully than is now generally done the immunopathology as just described with the clinical lesion.

Simple Allergic Conjunctivitis

There appear to be three definite immunopathologic types of allergy in conjunctivitis—the wheal type, the dermatitis type and the bacterial type.

(1) The Wheal Type. This conjunctival inflammation is best exemplified in hay fever which is a spontaneous hereditary allergy. It is mediated by the so-called skin-sensitizing antibody which has attached itself to cells of the mucous membrane of the eye, nose and bronchi, and to the skin. The clinical as well as the test reaction is an *immediate* one with hyperemia and edema. The common allergens are those of the air-borne group, pollens, animal danders, mold spores and various dusts. Also in certain cases foods, as egg and milk, may cause the same immediate edema reaction, but usually the eye reaction is only a minor part of a general systemic reaction with urticaria, asthma, vomiting and edema of the face, lips and tongue.

Ordinarily this simple non-infective conjunctivitis is acute and periodic depending on the allergen contact, but it may continue for long periods when the contact with the allergen is continuous and prolonged. In such cases the conjunctivae may show clinical evidence of organic tissue change, such as blepharitis. I recall the case of a child with asthma, coryza and conjunctivitis of four years' duration due to the nightly contact with a rabbit hair pillow. The skin test showed an immediate wheal reaction with rabbit dander. Removal of the pillow resulted in a prompt improvement of chest, nasal and eye symptoms, but it required six months for the eye to return to normal.

Conjunctival sensitization is made use of diagnostically in hay fever to demonstrate mucous membrane sensitivity when an instillation of the proper allergen into the eye will cause an immediate hyperemic reaction (Fig. 39). Also in cases of spontaneous serum allergy, the eye test, like the skin test, is positive, and this is one of the criteria of exquisite systemic sensitivity usually contraindicating any attempt at serum therapy.

In addition to this spontaneous type, a conjunctival sensitization may be induced artificially by the parenteral introduction of protein, such as an antitoxic horse serum giving rise to serum disease. A few days later when the urticaria has disappeared, a skin test with horse serum is immediately positive, and so also is the eye test, indicating the existence of a general anaphylactic type of sensitization which is of a relatively short duration, while the spontaneous sensitization is usually present for the major part of one's life.

(2) **The Dermatitis Type.** A somewhat similarly appearing conjunctivitis is that resulting from the dermatitic or exudative type of reaction to such drugs as atropine, pontocaine, anesthesin, mercury, arsenic and dyes (Lash-lure). These cases are usually distinguishable by the fact that there is an associated dermatitis of the skin surfaces of the lids, which is especially marked at the outer canthus continuing down the cheeks following the course of the tears which carry the drug. But there is also a difference from simple conjunctivitis in that there are often found regular rows of subepithelial follicles resembling those of trachoma. Histologically the epithelium shows extreme degeneration similar to that of the dermatitis. In most of these cases the skin patch test with the allergen shows the typical *delayed* exudative lesion indicative of a general skin allergy.

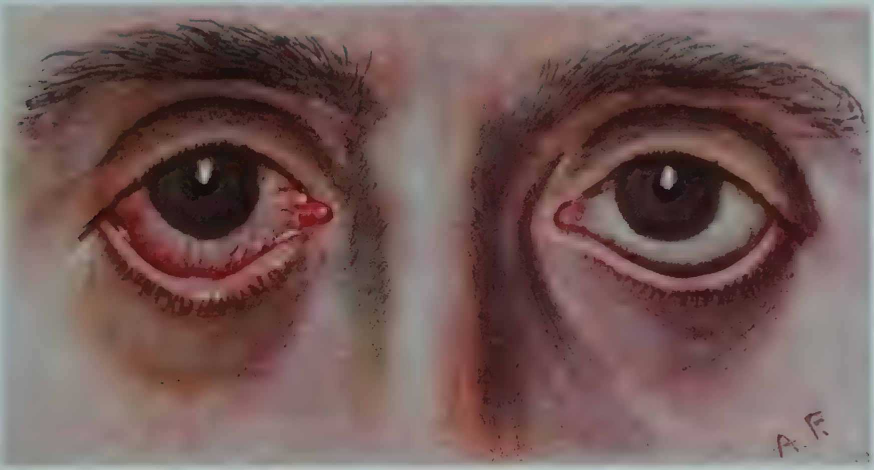

Fig. 39.—Ophthalmic test. The immediate edema-hyperemic reaction of moderate degree fifteen minutes after the instillation of timothy pollen extract into the eye of a patient clinically sensitive to timothy pollen.

Keratoconjunctivitis is the term applied to those cases in which the lesion also involves the cornea. This condition may arise from direct infection, such as the recent epidemic form due to a virus, but it may also arise from bacterial allergy and certain cases thus diagnosed appear to have the dermatitic type of sensitization. In this latter group would fall those observed by Rankine.[5] He reported on 1598 cases of keratoconjunctivitis observed over a period of two years among the spinners and "cake changers" in an artificial silk factory. This was regarded as an example of formalin sensitization, as theoformaldehyde is liberated in one of the steps in the manufacture of this product. At least two prolonged contacts were found necessary before symptoms would develop, the first of these the sensitizing, and the second the reacting, contact. Obviously therefore, the reaction was not due to a simple chemical or mechanical irritant. This idea is supported by the fact that there was perfect freedom from symptoms in 66 per cent of the workers having prolonged exposure. This type of reaction would appear to be of the nature of a dermatitis, not one of the wheal type, but no pathologic or immunologic studies were made and no associated skin lesions or other allergies were reported. However, O'Brien and Allen[6] have called attention to the frequent association of keratoconjunctivitis with dermatitis due to external contact factors as butyn, wool fat and dye.

(3) **The Bacterial Type.** We are not concerned here with infective conjunctivitis, epidemic or otherwise, in which any one of the pathogens may produce conjunctivitis by direct infection. In bacterial allergy the conjunctiva is not, primarily at least, directly invaded though in many cases secondary infection is bound to occur and aggravates but does not initiate the conjunctivitis.

It is not to be construed that all tissue reactions to bacterial products which are of an allergic nature are histologically the same; quite definitely they are not, neither is the immunologic basis identical. This is well illustrated by the pneumococcus sensitization in which the capsular substance of the organism gives an immediate urticarial wheal in the skin of the pneumonia patient, while the bacterial protein gives a delayed inflammatory reaction. Conjunctivitis due to bacterial allergy, however, is usually caused by a sensitization to the protein resulting in a delayed reaction of the tuberculin type.

An inflammation of the conjunctiva, generally persistent or recurring in its course with subjective symptoms of photophobia, lacrimation and irritation, is a recognized clinical entity. The eye cultures may be sterile and the scant secretion may contain eosinophils. A distant focus of infection is often discoverable. The basis for the allergic assumption may be found in a familial and personal history of past or present allergies as well as the presence of eosinophilia. The lesion very gradually disappears on removal of the focus, which usually is in the tonsils, teeth or sinuses. Clinically this type runs a chronic course though exacerbations frequently occur. When the cornea is involved a diagnosis of keratoconjunctivitis is made.

The following case suggests bacterial allergy as the basis for the conjunctival lesion.

A woman twenty-five years of age, recently seen, gave a history of repeated respiratory infections from childhood. Beginning when sixteen years of age she had a continuous inflammation of both eyes for three years. They were red and painful, with photophobia and lacrimation. Suddenly they cleared and remained clear for three years. Then followed a recurrence of a few months' duration, and again freedom for nearly one year. For six months prior to the present examination there had been continuous and severe inflammation of both eyes. Physical examination was negative save for evidence of hyperplastic sinusitis. Cultures of the conjunctivae were negative. A hemolytic Staphylococcus aureus and pneumococcus were recovered from the nasopharynx. Skin tests with important inhalants and foods were negative. She was then seen by Dr. Townley Paton who made a diagnosis of keratoconjunctivitis. She showed a spectacular recovery from the eye lesion during treatment with penicillin at the rate of 100,000 units a day given intramuscularly for ten days. A few months later the patient developed an acute sinusitis with the same eye symptoms which again responded to penicillin therapy. A staphylococcus was again cultured from the pus recovered from the antral irrigations.

The problem in such a case is to build resistance to the recurring staphylococcus infections, for which purpose autogenous vaccines and staphylococcus toxin are used in such doses as not to cause a symptomatic eye reaction. If this attempt is unsuccessful, then surgery may be required for the removal of the suspected focus.

Phlyctenular Keratoconjunctivitis

A modification of simple conjunctivitis is seen in the cases with phlyctenules.

Von Szily[7] developed the tuberculin allergy theory, in relation to the eye, which seems to be supported by the studies of Guillery[8] and particularly of Riehm,[9] who showed that tuberculin instilled in the eye of tuberculous animals produced a typical phlyctena. Other organisms, as the gonococcus, have been shown to produce the same lesion in cases of chronic gonorrheal arthritis. Riehm[10] reported that phlyctenules were produced by instillation of horse serum into the eyes of animals previously sensitized to the serum. Loddoni[11] confirmed this experimental work. However, it still needs to be repeated, because it is contrary to our present ideas of the pathologic conditions produced in this type of artificial sensitization to protein.

Bothman's[12] illustrative cases of phlyctenular lesions due to allergy to pollens and foods are reported with such brevity that they cannot be properly evaluated, but they are not convincing. For example, Case 15 "had red eyes beginning the end of May and lasting until the middle of September for two years." "The patient . . . .was strongly sensitive to several tree pollens and less so to ragweed." One must ask what was the allergen that caused the symptoms during the eight weeks from mid-June to mid-August. Certainly neither tree nor ragweed pollen was in the air.

While there is some evidence in favor of allergy as the basis for phlyctenular conjunctivitis, further study must be made to establish the fact as well as the type of allergy concerned. There is greater reason for the assumption of allergy to bacteria than that to inhalants and foods in these cases.

Vernal Conjunctivitis

Vernal conjunctivitis is an inflammatory reaction, usually binocular, in which symptoms appear in spring and summer though the lesion may persist throughout the year. It is more common in tropical and lower temperate zones, and is more frequent in the young (ages five to twenty years) and in males (Lehrfeld[13] gives 73 per cent).

The symptoms appear with the first warm spell in spring and continue until frost. There is photophobia, redness, tearing, itching, and a characteristic tenacious rubbery mucoid discharge in which eosinophils are abundant. There are two forms: (1) the palpebral, and (2) the bulbar or limbic.

(1) The palpebral type is the more common, and the tarsal conjunctiva of the upper lid is the principal seat of the lesion. The lower lid is rarely involved alone. At first, hard flat papillae appear with general hyperemia and the conjunctiva takes on a salmon pink color. Later the hypertrophied papillae coalesce to form the so-called "cobblestone" appearance, and in the more advanced stages there develops a cauliflower-like granulomatous lesion. This latter does not disappear in winter even though the patient may be symptom-free.

(2) In the bulbar or limbic type, crops of sago-like vesicles appear at the limbus and may surround the cornea with a ring of this hypertrophied tissue. The bulbar vessels are engorged. In winter this lesion may disappear.

The course of vernal conjunctivitis is given commonly as from two to four years in the textbooks on ophthalmology, while up to ten years is not rare, and some cases persist indefinitely. Corneal ulcer is a not infrequent complication.

Pathology. The essential lesion is one of epithelial proliferation and hyperplasia of the lymphoid and connective tissue, the tarsal plate being particularly involved. There is extensive infiltration with eosinophils and lymphocytes. In the bulbar type there is infiltration of plasma cells and eosinophils and marked epithelial proliferation.

Allergy and Vernal Conjunctivitis. It was natural that allergy should be invoked in explanation of this condition which has no known etiology, because of its summer appearance; a symptomatology grossly suggesting hay fever; its appearance in the same age group; and the presence of eosinophile cells in the secretion. While this evidence is suggestive it is only that, and further support for the allergy theory has been attempted.

Many efforts have been made to prove that pollen is the responsible factor, using the usual procedure of skin and eye tests with pollen extracts. The evidence incriminating pollen is meager, for even if some ophthalmic reactions to pollen have been obtained, the pollination season does not coincide with the duration of the eye symptoms, and this is a *sine qua non* for all allergic reactions. My own studies[14] of this condition have not supported the thesis that any air-borne substances alone or in combination such as pollen, mold spores, or animal and vegetable dusts, nor any foods, are etiologic factors. In this study of about fifty cases, since considerably enlarged by Barnard, there is reason to believe that allergy does explain the condition by reason of the fact that 50 per cent of the cases give a history of antecedent allergy, and the same percentage have past or present allergies. Hay fever as an associated allergy is not infrequent and was found in about 25 to 30 per cent of our cases, but its occurrence did not coincide with the duration of the active symptoms of vernal catarrh. Further support is gained for allergy by the presence of eosinophile cells in the mucoid discharge in practically all cases if repeatedly examined, as well as the common finding of a blood eosinophilia.

Most significant of allergy would be a symptomatic reaction in the eye resulting from the subcutaneous injection of an autogenous vaccine. That this does occur is illustrated in the case of B.F.

This boy, aged eight years, had typical recurring eye symptoms for four years. These began in March and lasted until fall. His father and sister have hay fever, the patient does not. On examination both upper lids presented typical cauliflower growths with characteristic exudate showing eosinophils. His tonsils had been removed. There was considerable adenoid and pharyngeal lymphoid tissue but nothing clearly operable. Eye cultures were negative. Nasopharyngeal cultures yielded pneumococcus, Streptococcus viridans and Neisseria catarrhalis. These organisms were combined in equal parts in a 1 per cent per volume heat-killed vaccine. Under vaccine therapy his symptoms were much improved during the first summer. The following year with injections of vaccine he did well up to the first of July. Then after a six weeks' lapse of treatment a repetition of the previous injection produced an acute conjunctivitis with typical symptoms of photophobia, lacrimation, congestion and discharge. Again treatment was omitted for eight weeks, this time on account of mumps. Then in the middle of October, while free of eye symptoms, an injection of the same dose of vaccine reproduced the symptoms. Each time the acute flare-up began at the end of twenty-four hours and lasted four days. Such symptomatic reactions certainly suggest allergy of the bacterial type.

Bacterial Allergy Theory. Vernal catarrh is not interpretable as an allergy of the immediate wheal type like hay fever, for the histology of the lesion is not such as can be produced by that reaction as there is tissue hyperplasia which does not result from wheal formation. A close analogy to the pathology of the mucous membrane in vernal conjunctivitis is found in the mucous membrane of hyperplastic sinusitis which I have interpreted as an allergic reaction to bacterial products (see Chapters 9 and 12). This theory as to the pathogenesis of vernal catarrh has not yet received recognition nor confirmation but is worthy of consideration.

Acting on the above assumption these patients in my clinic have been treated by the elimination of foci of infection which are practically always found, and by the use of vaccine therapy with encouraging results. The final proof of the correctness of the theory has not yet been obtained, but support is offered by the symptomatic reaction to vaccine.

as in the case just cited. The most that can be said is that a rational immunopathologic relationship has been suggested.

Diagnosis. The diagnosis of vernal conjunctivitis in its initial phases is difficult, for it may readily be confused with simple acute conjunctivitis of any cause. In the established cases the history of summer exacerbations, the intense itching and photophobia, the characteristic appearance of the conjunctiva, and the rubbery mucoid discharge loaded with eosinophils is sufficient to establish the true nature of the disease. Vernal conjunctivitis should be differentiated readily from trachoma, symptoms of which are not related to the season, and in which there is absence of itching and eosinophilia. Pannus, not found in vernal catarrh, is frequent in trachoma.

Treatment. Symptomatic therapy calls for the use of an alkaline solution as recommended by Lehrfeld.[15]

Sodium carbonate (monohydrated)	5 to 10 grains (0.3 to 0.6 gm.)
Water	1 fluid ounce (30 ml.)

Three or four drops instilled into the eye four times a day.

Cold boric acid solution should be used as an eye wash frequently through the day. Petrolatum or carbolated petrolatum should be applied to the lids at night. When secondary infection has taken place, as is frequent, some antiseptic such as aqueous mercurochrome (2 per cent) or merthiolate (1:10,000) should be used once or twice a day provided there is no sensitization to mercury as shown by previous patch test. Local anesthetics should be used with care as an allergic dermatitis may develop to synthetic drugs based on cocaine, although cocaine itself seldom gives rise to dermatitis. The following prescription is safe for occasional use:

Cocaine hydrochloride	0.1 gm.
Boric acid	1.0 gm.
Epinephrine hydrochloride 1:1000	8.0 ml.
Rose water to make	32.0 ml.

Eye drops:—One or two drops in each eye when inflamed.

Specific therapy is directed against the cause. On the basis of a probable bacterial allergy, foci of infection should be sought and removed if possible. Vaccine therapy, preferably autogenous, or a filtrate containing staphylococcus exotoxin may be used. If the patient has an associated allergy such as hay fever he should receive appropriate specific therapy. The special technics of the ophthalmologist such as radium and carbon dioxide ice need not be considered here.

Scleritis and Episcleritis

The inflammatory reaction in the sclera usually associated with a similar lesion in the overlying conjunctiva is persistent and recurring. Balyeat and Rinkel[16] have reported cases of episcleritis associated with urticaria due to food. One of my patients with a family history of allergy was interesting in that first he had urticaria, then polyarthritis, and finally episcleritis. Eye cultures and skin tests were negative. There was a hemolytic streptococcus infection of the tonsils. Following a tonsillectomy and penicillin therapy for ten days there was a gradual improvement of all symptoms; a few weeks later, on the second day after an injection of 0.1 ml. of an 0.01 per cent autogenous vaccine made from cultures of the tonsil tissue, there developed a symptomatic reaction of severe grade affecting joints, skin and eye.

In view of the absence of specific etiology, the association with urticaria and other allergies and the hereditary history as brought out by Heinonen,[17, 18] allergy may be assumed to explain certain of these scleral inflammations with foods and bacteria acting as the allergens.

Allergies Affecting the Cornea

Interstitial Keratitis. Simple keratitis is frequently seen associated with conjunctivitis of allergic origin as previously mentioned. There is reason to believe that the parenchymal (interstitial) involvement in certain specific infections as syphilis (Wessely[19]) and tuberculosis (Löwenstein[20, 21]) is allergic in nature in some of the cases. This is indicated in syphilis by the lack of response to arsenic therapy occasionally seen in keratitis; in fact there may be an acute exaggeration of the lesion, a sort of Herxheimer reaction of the eye, which may be interpreted as an allergic response of sensitized cornea to trypanosome substance released in the circulation as a result of the arsenic effect on the organism.

Wessely[19] studied this condition in the experimental animal by injecting heterologous serum into the lamellae of the cornea. The irritative reaction promptly cleared, but after two weeks an inflammation set in and cleared spontaneously in two weeks. A later injection in the fellow eye produced an immediate corneal lesion. This Wessely termed keratitis anaphylactica, assuming that the first injection had produced a general sensitization of the animal. This work supports the earlier findings of Kummel[22] and of Krusius[23] and was confirmed by the later studies of von Szily.[24]

Corneal Ulcer. There has been an attempt to interpret certain cases of suppurative keratitis as allergy. The illustrative cases which are cited in the literature were reported by Parlato[25] (1934), by Bourbon,[26] by Moran[27] and by Block[28] (1935). Parlato's case was one of sensitization to orris root causing conjunctivitis. The skin test to orris root was positive. In no way can one conceive that the edema or wheal type reaction causing conjunctivitis could produce a pustular conjunctivitis and keratitis (ulcer) except as a result of secondary infection. The ulcer itself was not an allergy. The same reasoning applies to the reported cases with sensitization to paraphenylendiamine. This allergen produces the lesion of dermatitis and the suppurative infection is secondary. The question may be academic, but if one attempts to explain lesions on an allergic basis they must be seen in their true light. The suppurative infection would not occur without the preliminary allergy, but still the ulcer itself was not an allergy. The immuno-pathologic mechanism and relationship must be considered and observed.

Allergies of the Uveal Tract

Iritis and Uveitis. The part played by allergy in the inflammatory reactions of the iris and uveal tract has been extensively investigated clinically and experimentally. For purposes of brief discussion the cases divide themselves into two groups: first, those due to inhalants and foods (protein sensitivity) and to drugs; second, those due to bacterial products.

With regard to the first group Bothman[29] has reviewed the literature to 1941 and presented cases of his own. A critical inspection of the records as presented does not permit a positive conclusion but leaves considerable doubt as to any allergic factor in the cases cited.

As to bacterial allergy the experimental evidence is convincing that the eye may be sensitized. Swift et al.[30, 31] Julianelle,[32] and the Seegals[3, 4] confirm one another in their studies on experimental animals. Ocular tissue could be made hypersensitive so that later contact with the specific organism produced the ocular reaction.

Clinical confirmation of this experimental work is hampered by the hazards involved. Skin tests with bacterial substances are worthless in man on account of the frequency with which reactions are obtained in supposedly normal subjects. There are no adequate controls, for most adults have been subjected to previous infection of one sort or another. However, the production of a symptomatic reaction twelve to forty-eight hours after an autogenous vaccine injection is good evidence, especially if it can be repeated. Otherwise, in man, one must at present be satisfied only with the evidence obtained through a statistical evaluation of the comparative results secured from a group of patients treated on a basis of bacterial allergy, in contrast with the results from patients treated symptomatically or by another form of therapy not based on infection. Such evidence is not now available.

On the thesis of bacterial allergy the proper procedure is to search for foci of infection throughout the body, especially in the oral and upper respiratory tract, also in the gallbladder, kidney, appendix and genital tract. Any focus of infection should be removed. If this is not feasible, treatment with autogenous vaccines or antibiotics may be employed.

Sympathetic Ophthalmia. This is a relatively rare condition. Following trauma, usually a perforating wound of one eye, there may develop after weeks or months an inflammatory reaction in the uninjured eye provided the injured eye has not healed and shows signs of iridocyclitis.

The histologic lesion of the injured eye is characteristic and from the point of view of allergy one of the distinctive evidences is the presence of epithelioid and giant cells in the granulomatous masses of the uvea, which are described by Samuels[33] as "larger than lymphocytes, have an oval vesicular nucleus and a protoplasm staining with eosin."

The purpose here is merely to outline the basis for the concept of allergy in explanation of the lesion in the primarily injured eye and later in the other or sympathizing eye where the destructive infiltration is essentially identical.

Elschnig[34] was the first to attempt an explanation of this type of ophthalmitis on the basis of anaphylaxis. Many others have worked in this field, but Woods[35] has been foremost in the development of the theoretical and practical aspects. As Woods concisely states it, "In this theory it was assumed that an injury to the exciting eye resulted in an absorption and general dissemination of the uveal pigment, which produced a hypersensitivity of the organism as a whole and especially of the homologous organ, the fellow eye. Continued absorption of this uveal pigment from the exciting eye resulted in allergic intoxication of the sensitized tissue of the second eye, manifested clinically as sympathetic ophthalmia."

In the first place uveal pigment was proven to have antigenic properties by the technic of complement fixation, and this protein, like lens protein, was tissue- or organ-specific, not species-specific. In practical application the results of Woods' studies indicated that the presence of complement fixation antibodies, found only in healed cases, indicated "immunity" rather than sensitization which caused persistent inflammation of the eye and prevented healing. Interesting purely as an immune response, this test was later discarded on account of technical difficulties in favor of the intradermal test with pigment solutions first reported by Woods[36] in 1925, and again by Little[37] in 1933. In this test 0.1 ml. of varying dilutions of the pigment solutions is injected. There is no immediate urticarial wheal as in hay fever, but tests are read from twelve to forty-eight hours and positive reactions usually appear in twenty-four hours. They consist of an area of redness and infiltration about the test site, in other words, a late reaction with a striking resemblance to a positive tuberculin test. The results of the test are interesting. As Woods[38] reported in 1936, "All patients with active sympathetic ophthalmia, twenty-two in number, gave positive reactions to the intracutaneous injections of uveal pigment." Two healed cases were skin test-negative. The test was also positive in a few cases of long standing non-infectious recurring uveitis, a condition which Woods terms allergic endophthalmitis dependent on pigment allergy.

Friedenwald[39] has supplied histologic evidence of the existence of immune activity in the skin of these hypersensitive patients by the demonstration of pigment phagocytosis in tissue sections of the reacting area best seen fourteen days after the skin test. "The whole area is infiltrated with epithelioid and giant cells full of phago-cytosed granules." The picture is entirely different in non-sensitive individuals. In the eye lesions in sympathetic ophthalmia this same phagocytosis of pigment granules is observed, and the lesion of the eye and of the skin is quite the same.

Treatment by injection of uveal pigment has been carried out in an attempt to "desensitize" patients, but the results are not too convincing in the small number of cases observed, for the favorable outcome in 70 per cent as reported by Woods[38] is not enough greater than the 68 per cent recorded by Verhoeff and Irvine[40] on patients treated according to an entirely different theory with diphtheria antitoxin.

The situation today stands thus: Allergy to uveal pigment has been proven to exist, but that this is the cause of ophthalmitis in whole or in part has not been proven. As Woods[38] puts it, allergy "lays the necessary foundation picture." The spark that sets off the inflammatory reaction is speculative and can only be settled by further experimental work.

Endophthalmitis Phaco-Anaphylactica

The clinical observation of an inflammatory reaction in the eye following trauma to the lens or in cases in which lens substance remained after operation for cataract led Verhoeff and Lemoine[41] to the theory that this reaction in non-infected eyes was caused by the development of a sensitization to lens protein. This lesion they termed endophthalmitis phaco-anaphylactica. It had earlier been shown by Uhlenhuth[42] that lens protein was antigenic and that it, like uveal pigment, was organ-specific, not species-specific.

Using lens substance for intradermal tests Verhoeff and Lemoine[43] found that patients who developed endophthalmitis after operation gave positive skin tests. No patient with a negative skin test developed the inflammation. Various observers obtained conflicting results. Burky and Woods,[44] with a special preparation of the protein, found persons with normal eyes entirely negative, while eleven of sixty-four cataractous patients gave a reaction on skin test. Eight of these developed intraocular inflammation. Those in whom all lens substance was removed at operation had no reaction, and presumably this is readily explained by the fact that they had no lens substance with which to produce a sensitization and the ensuing reaction. It is not to be expected that all persons exposed to lens protein will become allergic to it nor that all who are skin-sensitive will develop the eye inflammation.

Subcutaneous injections of lens substance have been used for purposes of "desensitization" in patients giving positive skin tests before opertion. Although it is considered good practice to use lens substance therapy after operation if inflammation occurs there is little convincing evidence of satisfactory results. Apparently it has never been observed to produce harm.

Cataract

Since Rothmund[45] called attention to the occurrence of cataract in connection with a peculiar atrophic condition of the skin, there have been other additions to the literature on this subject. The cases recorded under the term *Rothmund's syndrome* are in children or young adults. The cataract is generally bilateral.

A similar condition beginning in the adult in the third or fourth decade with cataractous lesions and atrophic skin which has a tendency to ulceration has been called *Werner's syndrome*. Somewhat closely related to these cases are those described by Andogsky[46] in 1914. He applied the term *cataracta dermatogenes* to the small group he reported. In these patients, what was termed "chronic eczematoid skin lesion" had been present from childhood, whereas the bilateral cataracts did not develop until the third decade. A number of cases have been reported since that time, some of them called *cataracta allergica*, and this whole matter has been recently reviewed by Thannhauser.[47] The extensive degenerative features in these cases described cannot satisfactorily be regarded as based upon allergy. Thannhauser expresses his opinion as follows: "For the pathogenesis of Werner's syndrome and Rothmund's syndrome a purely ectodermal dysplasia as well as primary endocrine functional disturbance is rejected. The recessive heredity of both syndromes suggests as an explanation for its etiology the existence of multiple germ plasm defects manifesting themselves in abiotrophic features of various organs at different periods of life."

Of course it was the association with what has been called "eczema" that induced the thought that the cataract was also an allergic response to the same factor which caused the skin lesion. Daniel's[48] report of three cases is quite typical of the contributions in general. In Case 1 a girl, seventeen years of age, had bilateral cataract, dermatitis and allergic rhinitis. "Eggs, milk, house dust, ragweed, corn pollen, cottonwood, silk, and dyes seemed to cause the most marked reactions." It is stated that direct and indirect skin tests were positive to these allergens, but there was no definite evidence presented to show that contact with any one of them reproduced one or another of the three clinical diseases. The combination of cataract with dermatitis is not to be wondered at in view of the relative incidence of each condition, but the frequency of the association is not such as to be statistically significant; at least no such evidence has been presented. Woods,[49] with his extensive clinical experience, when discussing Daniel's presentation says, "I myself have never seen patients with this particular syndrome." Bothman[50] also states that he has not seen a cataract that he believed was of allergic origin. Over the course of the years I have studied several hundred cases of allergic dermatitis in this early age group, and in no instance has there been evidence or a complaint of failing vision indicating the presence of cataract.

No sound evidence has yet been presented to warrant the inclusion of cataract as a manifestation of allergy when there are so many nutritional and hereditary factors that afford a better explanation.

Retinal Lesions

Lesions of the retina due to edema, hemorrhage or inflammation may be readily hypothesized as allergy on the basis of analogy, but this may be proven only with difficulty. Certainly, patients with urticaria and angioedema are entitled to an edematous lesion of the retina as easily as one of the brain or gastro-intestinal tract. Retinal edema of allergic origin is exemplified by such cases as those of Bedell[51] and of Bothman[50] which followed serum disease, as well as those of Williams[52] (pork-insulin) and Wiener[53] (tricophytin). As certain purpuras are definitely allergic there is also ground to believe that a hemorrhage of the retina is as possible as one of the intestine or bladder.

Presumptive evidence would be based upon a demonstrable allergic constitution of the patient through familial incidence or personal allergies, or by the definite relation of the condition to certain out-of-the-ordinary events as the previous injection of serum or biologicals. However, many of the cases as presently recorded do not measure up to proper standards for satisfactory evaluation. The effort should always be to disprove rather than to prove a thesis of allergy, and the basis for an assumption of sensitization in clinical reports should be clearly stated. There is very little indication of this in many case reports.

Other Lesions

Lesions of the ocular and optic nerves are a part of neurologic allergy (Chapter 19).

Lesions of the lids—angioedema and dermatitis—are allergic dermatoses. (See Chapters 13, 14, 15 and 18.)

Summary

There is no doubt that the concept of allergy offers a satisfactory explanation of many lesions involving the eye and its appendages.

An allergic diagnosis as well as treatment must be undertaken only in conjunction with an ophthalmologist. One should be fully aware of the limitations as well as the possibilities afforded by such a study.

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25. *Allergy of Infancy and Childhood*

ROBERT CHOBOT

Introduction

ALLERGIC manifestations in infancy and childhood, while they have some features that are particular for this age group, are none the less generally and fundamentally the same as those occurring in adults.

Pediatric allergy should have special appeal and interest as children respond to proper care and management more readily than adults, and because the allergic conditions have not reached the stage of chronic irreversible lesions nor should this be permitted, for such changes occur slowly.

Most of the points reviewed here have been discussed in previous chapters to which reference will be made, but some facts need more elaboration.

Infants are not born sensitive as far as our evidence exists today. The studies of cord blood[1, 2, 3, 4,] have not shown a single case in which reactions were obtained on passive transfer to normal human skin. This means that although protein antigens may have passed the placental barrier no active sensitization has been developed by the fetus, and there has been no passive sensitization with the sensitizing antibodies of an allergic mother. This is strikingly different from results obtained in guinea pig experiments by Rosenau and Anderson[5] and many investigators[6, 7, 8, 9] since their time. The inferences of Ratner, Jackson and Gruehl[8] on this are not borne out by existing data.

Infants develop a sensitization shortly after birth, exactly how soon is not definitely known, but allergic symptoms have been noted in babies a few weeks, generally a few months old. The earliest sensitizations are to foods such as eggs and milk, probably because these are the foods with which contact is established early in life. In almost all these early allergies the hereditary factor is active, and it was shown by Cooke and Vander Veer[10] that babies with a familial history of paternal and maternal allergy develop clinical symptoms at a much earlier age than those in whom the inheritance is unilateral (see p. 13).

The hereditary factor seems to be one of a tendency or capacity not a sensitization itself, for the allergen and the symptom in the child are more often different from than identical with that of father or mother. What determines the particular allergy in the particular child is not known, for the infants do not necessarily become sensitive to those foods or inhalant substances with which they have the greatest contact.

Personality Trends in Allergic Children

For many years it has been a popular conception that allergic children and adults possess superior mental traits, which for a time were believed to result from the allergic constitution. The literature contains many studies in children's personality. Balyeat[11] in 1929 strongly supported the theory of the superior mental ability of the allergic person. He based his conclusions on the results of the Otis self-administering test, which was given to eighty allergic and eighty non-allergic children. Stokes[12] described the child with neurodermatitis as ceaselessly active, precocious and egocentric. Clarkson[13] found intensification of emotion and retreat into illness, and he feels that in some children asthma is an expression of a definite psychosis. Oberndorf[14] holds that asthma is a manifestation of a conflict in the fields of emission and domination and submission, unconscious masculinity and conscious femininity. Reese and De Cellis[15] found allergic children to be more descendant and extroverted and unstable than the normal child. Children with skin allergies exhibit more of this type of psychic make-up than those with asthma.

Chobot, Spadavecchia and De Sanctis[16] studied 169 allergic children and attempted to compare their mental and emotional pattern with that of a normal group. They found that the allergic children showed no direct evidence of specific proficiency or deficiency in any field of educational endeavor, but varied in their abilities only according to their mental and educational status, just as the normal children did. The allergic children were neither retarded nor advanced as compared with a group of normal children. The allergic girls were more emotionally stable and better adjusted to their environment than allergic boys. The allergic children showed all degrees of ascendancy and submission, introversion and extroversion, the tendency being slightly toward submission and introversion for the girls as a whole.

There is, therefore, no preponderate evidence to show that psychic disorders are etiologic factors in the production of the syndromes found in the allergic child. The majority of psychiatrists do not believe in a personality or psychogenic defect in the allergic person. It is, on the other hand, important to realize that psychic factors can affect the allergic child or adult just as much as they can the non-allergic one, and they must be recognized as factors in the child's environment.

Bone Scorings and Their Significance in Allergy

The significance of bone scorings as a diagnostic aid in the allergic child was the subject of much work by Todd[17] and his associates. They described a type of skeletal pathology demonstrable on roentgenogram, which they believed to be characteristic of allergy in children. Todd interpreted the transverse markings in the bones of growing children as evidence of increased calcium deposition due to temporarily diminished growth resulting from the nutritional disturbances associated with gastro-intestinal allergy. They thus represented periods of diminished growth. Cohen and Friedman[18] suggested the use of roentgenograms showing scorings as an index of adequate control of gastro-intestinal allergy. Children whose bones showed no scorings were not placed on dietary restrictions.

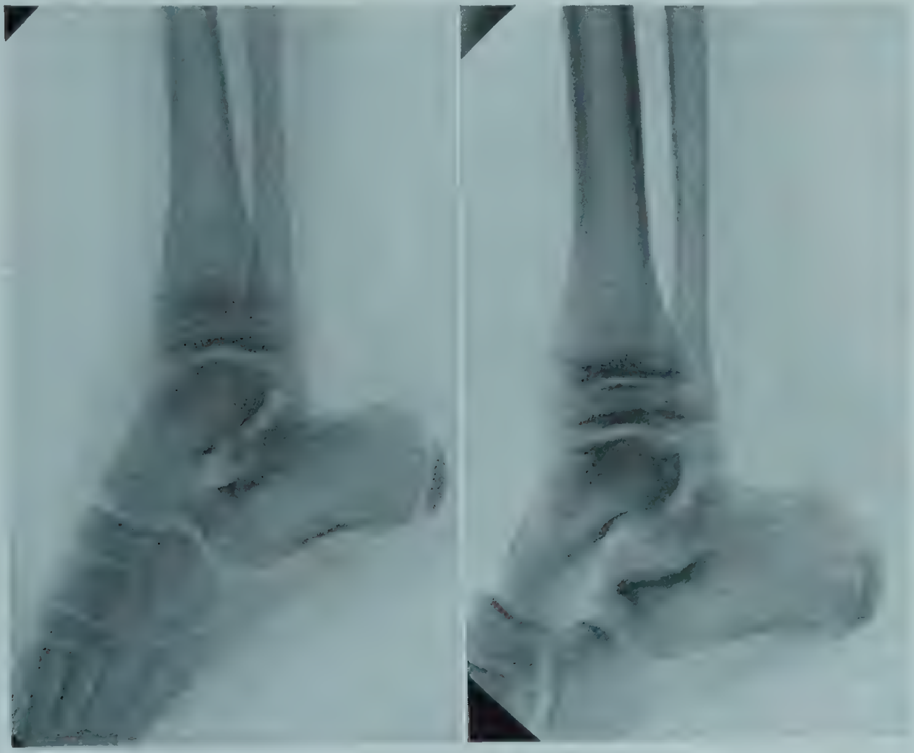

Fig. 40. Fig. 41.

Fig. 40.—Both distinct and faint scorings in tibia and fibula and in the radius in child aged seven years. More marked in tibia and fibula.

Fig. 41.—Same patient. No attacks of asthma for the past three years. Scorings present in tibia and radius. (J. Allergy, *8*:588, 1937.)

Bone scorings have been recorded by many observers. Köhler[19] ascribed them to delays in bone growth as a result of infectious diseases. Phemister,[20] Park et al.[21] and Caffey[22] have described scorings due to various causes. Eliot, Souther and Park[23] offered a rather extensive study concerning the significance of transverse lines in cases of rickets. Chobot and Merrill,[24] using Todd's technic, studied allergic and non-allergic children and were unable to correlate the incidence of bone scorings with the allergic state. (Figs. 40 and 41.) They pointed out that this transverse scoring is not diagnostic of allergy, but occurs in growing children and is found secondary to starvation, dehydration, acute infections or deficiency diseases. They were also able to demonstrate transverse bone scoring in gorillas. They concluded, therefore, that bone scorings cannot be considered diagnostic of the allergic state.

The Allergies of Infancy (One to Three Years)

There are three allergic conditions that are frequent in the first three years of life:

1. Acute systemic reactions.
2. Allergic dermatitis (infantile eczema).
3. Asthma.

1. Acute Systemic Reactions. These acute allergies are practically always the result of a food allergy of the immediate edema type. Certainly they are not rare but neither can they be considered common, and probably the incidence is much less than 0.1 per cent of the total infant population. Egg and milk are the most common allergens but occasionally one meets a case clinically reactive to mustard or to fish, usually in the form of glue. Wheat allergy is very rare. The systemic reactions are acute following contact with an allergen; there is edema of lips, face and tongue, vomiting, urticaria, asthma, abdominal pain and diarrhea.

Usually these sensitizations of infancy are lost spontaneously by the age of five or six years, but if maintained beyond this age they usually persist through adult life. Treatment by injection or by the so-called drop method is often given credit for the loss of sensitivity for which nature alone is usually entirely responsible.

2. Allergic Dermatitis. This condition, which for years has gone by the name of infantile eczema, is a characteristic exudative lesion of the skin, usually of the face and scalp, but it may be disseminated over the body. The majority of these cases run a self-limited course. Most of these infants have a familial history of allergy of one sort or another. Many of them, about one-half, give cutaneous wheal reactions of the immediate type to many allergens, especially egg and milk, but also to other foods and inhalants. The significance of these wheal reactions is not known for most of the allergens which elicit them give rise to no clinical symptoms in the infants. The fact that agents giving the immediate wheal reactions have no causal relation to the exudative lesion of the skin is discussed in Chapter 13. The importance of this conception is evidenced by the fact that the severe dietetic restrictions which have led to athrepsia in many of these infants are usually not warranted, are not beneficial and should not be imposed. While the causes of dermatitis of infancy are not yet clear, the general condition of these patients can be improved by proper feeding, that is, not withholding food unless there is a positive indication.

3. Asthma. In infants, except for the rare case in which dyspnea results as a part of an acute systemic food reaction, the one major etiologic factor for asthma is infection. This is discussed in detail in Chapter 7.

Dyspnea in the infant should always make one think first of thymic enlargement and rule it out.

The Allergies of Childhood (Three to Thirteen Years)

At times the allergies of childhood are a carry-over from infancy but, as has been said, usually the early sensitizations undergo spontaneous cure. This does not mean that the allergic infant ceases to be an allergic individual, for the fact is that over one half of them acquire a clinical sensitization of the same or different type but to a different allergen. Food sensitizations occupy a very slight place in this age group, while the inhalant allergens come to the fore and dominate the picture with infection occupying an important but still a secondary role.

The commoner clinical allergies among children are: allergic coryza, seasonal and perennial, asthma and dermatitis. Urticaria and angioedema are relatively much less frequent but of course important in the individual case when they occur.

The causes, management and treatment of coryza in children are the same as for adults. (See Chapters 10 and 12.)

Asthma in Childhood. Of particular importance is the diagnosis and management of asthma in this age group. (See Chapters 6 and 7.) There is a mistaken notion that children will outgrow asthma; nothing could be further from the truth. These children should be diagnosed and treated as soon as there is a suggestion that asthma may develop. This can often be foretold in children allergically predisposed by heredity who have frequent respiratory infections and persistent cough. At first the cough is not accompanied by dyspnea or wheezing and may be of such a paroxysmal character that pertussis is suggested but this may be ruled out by the absence of lymphocytosis.

Of importance from a differential point of view, are the following:

Tracheobronchitis. Tracheobronchitis is sometimes difficult to differentiate from asthma, but there is more infection than is commonly seen in the ordinary asthmatic attack. The persistence of fever and leukocytosis, and the absence of paroxysms of dyspnea and blood eosinophilia, help one differentiate the two conditions.

Foreign Bodies. Foreign bodies in the trachea or bronchi are frequently overlooked. The history is all-important. Roentgenograms may be of help, but if the seed or piece of nut or cartilage is translucent the roentgenogram may be entirely normal. These children are apt to have a persistent brassy cough. There may or may not be wheezing, depending on the location of the foreign body. If there is any suspicion of a foreign body a bronchoscopy should be done. If the body obstructs the entrance to a lobe, the air distal to it is absorbed, with resulting atelectasis and elevation of the diaphragm. The heart and mediastinum are drawn to the affected side. If the foreign body acts as a ball valve allowing an ingress of air, but preventing its escape, the result is a marked emphysema resembling a cyst. A foreign body may cause an area of increased pneumonitis, or the result may be a lung abscess.

Tumors. Tumors of the lung are not too uncommon in occurrence; however, they can give symptoms of respiratory dyspnea. The differential diagnosis is made by adequate x-ray examination. Bronchogenic sarcoma and tumors of the mediastinum are those usually seen. Tumors of the trachea or larynx are occasionally seen, and depend on bronchoscopic examination for differential diagnosis.

Enlarged Thymus. Shadows of an enlarged thymus are not seen as frequently in pediatric practice as heretofore. The condition is being recognized shortly after birth as a result of routine roentgenogram and such patients are given adequate x-ray therapy. Pressure of an enlarged thymus gland on the bronchial tube produces a sound similar to that heard in an asthmatic child. A physical finding which serves in good stead is the stertorous character of the breath sound, and the absence of moisture in the affected lung. Occasionally an asthmatic child is seen with an enlarged thymic shadow, and yet his asthma is purely allergic and the enlarged thymus is entirely an accidental finding. A good rule is never to start tests on any child with this type of shadow until the thymus has been reduced in size with adequate roentgen ray therapy. The reason is that a constitutional reaction in any infant with an enlarged thymus carries added dangers resulting from status lymphaticus.

Substernal Thyroid. Substernal thyroid is difficult to diagnose only when it is extremely large and capable of considerable bronchial compression. Most of these enlarged thyroids are congenital in character and discoverable by roentgen rays.

Tuberculosis. There are marked differences between the progressive forms of tuberculosis in infants and in adults. Tuberculosis of childhood may have its site of origin anywhere in the lungs. Caseation as a rule is prominent and fibrosis is not marked. The lymph nodes in children are usually markedly involved. In the adult the upper lobes are usually the site of origin, and there is considerable fibrosis. Lymph node involvement is not as marked in the adult as in the child. Miliary tuberculosis is much more common in childhood than in adult life, probably due to the fact that lymph nodes erode into a bronchus and so spread the tubercle bacilli to other parts of the lungs.

Tuberculosis in asthmatic children is usually miliary in character, and the differentiation is made by adequate roentgenographic examination. It is important to remember that both conditions can exist in the same patient but tuberculosis in asthmatic children is not common. However, in any patient with tuberculosis, care must be taken to evaluate the amount of dyspnea that is due to the pulmonary dysfunction. Enlarged tracheobronchial glands due to tuberculous involvement occur, and the possibility must always be borne in mind that the diagnosis should not be made from roentgenograms alone. Such glandular enlargements are common in asthmatic children without evidences of tuberculosis, and are frequently the result of drainage from infected foci in the upper respiratory tract. The diagnosis of hilar tuberculosis depends on cough, a rise in temperature, dyspnea, anorexia and a positive tuberculin test.

Bronchiectasis. Bronchiectasis is a rare occurrence in asthmatic children. Occasionally one does see a case and the diagnosis is dependent on roentgenograms following intrabronchial lipiodol. It is extremely important to remember, however, that a patient with infective asthma producing large quantities of sputum, whose roentgenograms are entirely normal, should be examined bronchoscopically with enough lipiodol injected to clearly outline the entire bronchial tree. I reported one such case several years ago[25] in which the diagnosis would never have been disclosed without the injections of lipiodol, as all direct roentgenograms were normal (Figs. 42 and 43).

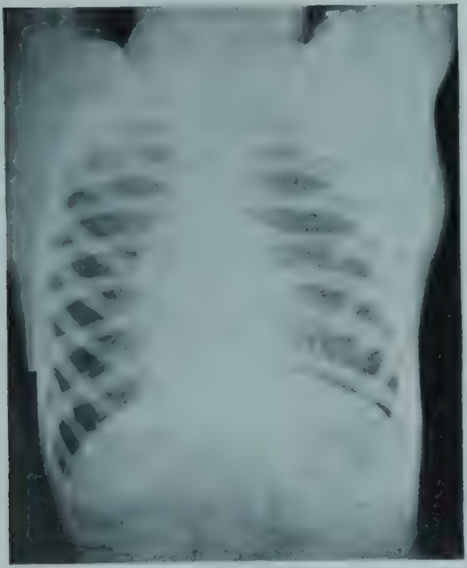

Fig. 42.

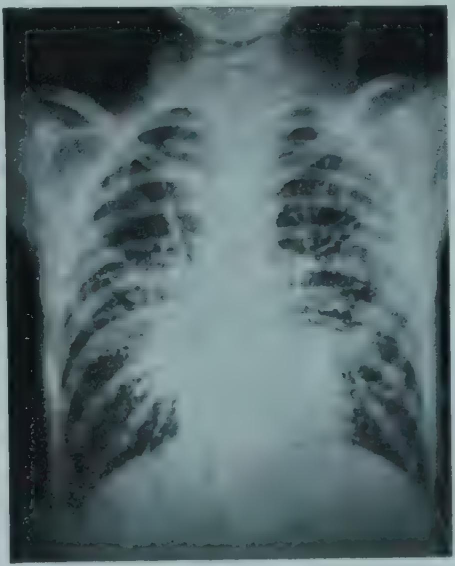

Fig. 43.

Fig. 42.—X-ray of the chest without lipiodol.

Fig. 43.—X-ray of the chest with lipiodol showing a bronchiectasis of the right lower lobe.

Löffler's Syndrome. Of special significance in children is the condition frequently spoken of as "Löffler's syndrome.[26] It occurs in allergic children, usually asthmatic, is characterized by an extremely high blood eosinophilia (10 to 60 per cent) and transitory consolidations of the lung. Some of the cases run a benign course. Others are associated with the pathologic changes characteristic of periarteritis nodosa or of disseminated lupus erythematosus. In general these cases fit into a picture of severe bacterial allergy.

Diagnosis of Allergy in Children

The history, physical examination and laboratory studies are as essential in infancy and childhood as in adults. The special technic of skin testing has a certain significance and should be done when required. Skin testing of infants up to five years of age is preferably done by the method of passive transfer.[27] The technic is described in detail in Chapter 31. As with direct tests this indirect method has its difficulties and its inaccuracies.

Chobot and Hurwitz[27] studied allergic children who gave 217 multiple positive direct skin tests to food. When passive transfer tests were done with these children's serums, only 93 of the 217 were found to be transferable. Of the ninety-three, only twenty-one were proven to have clinical significance. The 124 positive direct tests which were not transferable were analyzed; 101 had no clinical significance, and twenty-three (or 18 per cent) were found to be clinically important in spite of their failure to transfer.

To summarize: In a series of cases having positive skin tests to foods only 20 per cent of the tests were shown to have clinical significance; 18 per cent of those with skin reactions to foods that did not transfer gave symptoms on feeding, and only 22 per cent of the tests that did transfer were clinically significant.

Aside from demonstrating the fact that skin tests to foods, even in children, must be carefully correlated with the entire clinical picture, this work likewise shows that *the determining factor in the allergic child is one of cellular sensitization of the shock organ.* The circulation of skin-sensitizing antibodies certainly does not carry the significance that many observers have heretofore believed.

It is important to emphasize at this point that while there are sharp discrepancies between the importance of skin reactions to foods and their clinical significance, this is not so apt to be true in the case of the inhalant substances and the ability to transfer any reaction to one of the inhalant substances is more likely to be of significance than in the case of foods. However, even with the inhalants there are exceptions.

If there are inaccuracies to be found in the indirect testing, one must likewise acknowledge non-specific reactions which mean very little on direct testing.

The fact is that no matter what type of testing one employs, whether direct or indirect, one should be aware that the tests are after all only a means to an end, and that by themselves they prove very little. It is the clinical history that gives the clue to the sensitivities which the child possesses. The degree of sensitivity or the transferability of the skin reaction is only of academic importance, unless it can be definitely shown that contact with the offending food or inhalant is capable of precipitating the clinical syndrome in question.

The vast majority of food sensitivities in children are of the immediate type. It is wise to emphasize that a food sensitivity of the delayed variety and sensitivity of the immediate type can be demonstrated in the same child.

It is important to emphasize that indirect testing is of value, but that it represents, as does direct testing, only a diagnostic technic. Like direct skin testing, it must be confirmed by the clinical test of contact with the resulting production of symptoms.

Treatment

The principles of treatment for allergies in infancy and childhood are the same as for the adult, namely, avoidance of the allergen or corrective measures as immunization or, in the cases of bacterial allergy, the proper use of antibiotics.

In infants (one to three years) and regardless of the symptomatology, the principal allergens belong in two classes: (1) foods and (2) infection.

1. *Foods.* The chief known causes are egg and milk (casein and whey). Wheat is considered by many authorities as being of real importance but this is usually based upon a skin test reaction with an immediate wheal and not on confirmed clinical trial. Cooke may be quoted as saying that he has never seen a case of proven clinical sensitization to wheat though it may give a positive skin reaction. Other allergens less frequently met with, but clinically very important when they do cause reaction, are: nuts—peanut, brazil, coconut and almond—also mustard, cottonseed, flaxseed and fish. Fish does not have to be eaten as such but may be inhaled when it is cooked in the home or when toys containing fish glue are licked by the baby.

Once the allergen is definitely determined the difficulties are less than in childhood as the contacts in infancy are more easily controlled. The real difficulties arise in those clinically reactive to milk and egg. Other allergens when known are readily avoided.

A. THE MILK SENSITIVE INFANT. Most infants are allergic to the lactalbumin (whey) and not the casein but either or both may be causative allergens. The immunochemistry has been carefully studied by Wells and Osborne.[28]

The *whey protein-sensitive* patients may be fed on human, goat or mare's milk if available, because these proteins are specific and do not as a rule react in those sensitive to cow's whey, or one may use milk boiled in a double boiler for six hours or the commercially available evaporated (not dried) milk. Even this, according to Ratner,[29] should be boiled vigorously for five to ten minutes just prior to use. Evaporated milk is usually heated to 240° F. and vitamin C (50–100 mg.) which is destroyed must be added.

Soy bean milks* have been prepared. Hill and Stuart[30] suggested one (Sobee) which they state will maintain infant nutrition for periods up to one year. It should be precooked in a double boiler for forty-five minutes. It is not well tolerated by all infants according to Hill.[31]

The *casein-sensitive cases* are much more difficult to handle. The sensitivity is determined by direct or passive transfer test (immediate wheal) or by clinical trial. The difficulty arises from the fact that casein from milk of various animal species is antigenically identical as shown by Wells and Osborne,[28] and its antigenic property is not destroyed by heating to 100° C. for twenty-five minutes (Wells[7]).

These infants cannot be given any milk or milk products alone or in cooked foods. In such cases the soy bean preparations or gruels fortified with additional proteins, fats, minerals and vitamins may be used.

Various amino acid preparations are available for infants who cannot tolerate any milk or the soy bean foods. Hill[31] made a study of one such product† and found that it could be fed over relatively long periods with satisfactory weight gain. These food substitutes are non-antigenic and are derived from protein, usually casein, by enzyme or acid hydrolysis and contain all the ten essential amino acids. Great improvement in these foods will shortly be made, for the preliminary studies have contributed largely to a better appreciation of the fundamentals of nutrition. For a list of foods containing milk, see Chapter 28, p. 472.

B. THE EGG SENSITIVE INFANT. In the majority of cases the antigenic substance is contained in the egg white and rarely in the yolk. Some egg-sensitive cases also react to chicken and to chicken broth. I have never seen a mother who had great difficulty in avoiding egg in feeding her infant. However, one must be sure that with nursing infants the mother does not eat egg, for, as Donnally[32] showed, egg white may be secreted in breast milk under certain conditions. For a list of egg-containing foods see Chapter 28, p. 472.

One must today be on guard against any use of the newer virus preparations such as typhus and yellow fever vaccines made from organisms grown on chick embryo. Several serious accidents in egg-sensitive adults have already been recorded.

2. *Infection.* Allergies of all clinical types may result in persons with a sensitization to bacterial substances. This is true in children as well as infants. Treatment consists in:

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* Mull Soy, The Borden Company. Sobee, Mead Johnson and Company.

† Amigen Compound (Mead Johnson and Company).

(a) Removal of an existing focus, if possible.
(b) The use of vaccines, preferably autogenous, to promote increased resistance.
(c) Antibiotic therapy (penicillin) and sulfonamides especially useful in the acute phases of infection.

For details of therapy see Chapter 7 on Asthma.

In children (three to thirteen years) when *food sensitizations* exist the difficulties are greater but most children know from experience what they can and cannot take. As stated, most of the infant food sensitizations disappear spontaneously by the fifth year. Desensitization (so-called) by feeding or injection is rarely warranted but is often credited for what nature has done.

Greater difficulty arises today from the proprietary mixtures with inadequate labeling, i.e., butter substitutes containing cottonseed oil are antigenic for those exquisitely sensitive to cottonseed. Many such problems will disappear as food production becomes more normal again.

Infection in children is handled along the same lines as for infants. In general it may be said that the bacterial allergies are not properly recognized, appreciated or managed. Sinusitis in children is common, as Dean[33] and others[34] have shown, and is certainly a factor along with lymphoid hyperplasia of the pharynx, adenoids and tonsils. This has been discussed in detail in the several chapters on systemic diseases and especially on asthma. See Chapter 7.

Inhalant factors causing coryzal symptoms and asthma are important throughout childhood and especially after the fifth year. These are discussed in Chapters 6, 10 and 12.

Prognosis

In no phase of allergy are the results of proper therapy more gratifying than in pediatric practice. Even though sensitization cannot often be prevented, these patients can be managed through the important years of their growth and development. The prognosis is good for those that are properly directed.

It is a fallacy that children will outgrow their allergies. This is a belief too often followed and its practice frequently leads to serious difficulty.

Great caution must be used with regard to dietetic restrictions in the growing child unless they are proven to be absolutely necessary.

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Section VIII

ALLERGENS IN RELATION TO DISEASES OF ALLERGY

In the foregoing chapters on the systemic diseases of allergy the various allergens concerned have been discussed in relation to the particular disease. This section is merely a résumé of the previous chapters considered from the standpoint of the allergens and their relation to the various diseases.

All allergens react at the point of contact with and absorption by specifically sensitized cells. Those that are absorbed from areas of acute or chronic infection are carried to the sensitized cells of the various tissues through body fluids, blood or lymph, and therefore are often manifested by disseminated, multiple or associated lesions characteristic of bacterial allergy, as for example arthritis complicating chronic infective asthma.

Air-borne allergens are inhaled and naturally come in contact with the sensitized cells of the mucous membrane of the respiratory tract and are therefore important in the allergies of this area. Rarely, through external contact with the skin, they may cause a local cutaneous lesion.

Foods, drugs and biologicals may act locally upon the mucous membrane of the digestive tract following ingestion, and are frequent causes of widespread reaction after absorption into the blood stream whether taken by mouth or parenterally administered.

26. Bacterial Allergy

ROBERT A. COOKE

THOSE WHO are concerned with clinical allergy are constantly meeting cases in which the evidences of typical allergic diseases cannot adequately be explained on the basis of contact with protein substances inhaled or ingested or any allergen arising from without the body. Also, the history of acute infectious disease, as pneumonia, pertussis and measles, so frequently found as an antecedent to and in conjunction with asthma, rhinitis and urticaria; the occasional and prompt relief of long-standing allergic manifestations following drainage of or removal of an infected focus; together with the frequent reproduction of an allergic symptom following an injection of an autogenous, sometimes stock, vaccine; all of these occurrences cannot fail to impress one with the probability of a factor arising within the body and of a causal relationship of the infection to these allergic diseases. Such cases are today referred to as examples of *bacterial allergy*. Unfortunately, proof of bacterial allergy is not easy to obtain, for as yet there is no direct approach by any type of laboratory or skin test (but neither is there in many of the cases attributed to foods), and the conclusion as to a bacterial etiology is often indirect. However, this may be arrived at by the process of exclusion and by the history, as previously stated, and by the course of the disease so frequently exacerbated by intercurrent acute infection.

While more information is still needed, there has been a vast amount of experimental work done and a great deal of vital information has been accumulated since the turn of the century. It is necessary to review the more pertinent of these investigations and their present day interpretation.

Experimental Bacterial Allergy

Evidences of bacterial allergy were recorded long before the existence of anaphylaxis and allergy was appreciated, for Koch[1] had observed that the tuberculin reaction was a specific response in tuberculous animals. In their studies published in 1907, Rosenau and Anderson[2] reported anaphylactic shock in guinea pigs sensitized with extracts of colon bacillus, yeast, hay bacillus, anthrax, tubercle bacillus and typhoid bacillus. These findings were promptly confirmed by Kraus and Doerr[3] and Kraus and Holobut,[4] who established the additional evidence that sensitization could be transferred by the serum to normal animals.

Baldwin's[5] early work (1910) is important because he was the first to carry out experiments which indicated fundamental differences in two types of reaction in tuberculosis. Guinea pigs sensitized with filtered watery extracts of ground tubercle bacilli exhibited gross anaphylaxis on reinjection but did not show the tuberculin type of reaction in the skin. He used other technics for producing sensitization and his animals became anaphylactic but were non-reactive to tuberculin by skin test. The only way he could produce a tuberculin type of response was through active infection with tubercle bacilli.

The final and convincing proof that two different types of immunologic reactivity existed was supplied by Zinsser[6] (1921). Both the anaphylactic and the tuberculin types of sensitization could be produced in the same animal at the same or at different times, or one could be produced without the other. Anaphylaxis was the response to the protein of the tubercle bacillus, and the other was produced by active infection. Later work has shown that active infection is not essential to the tuberculin reaction. It also supports the separation of the two types of response into bacterial anaphylaxis and tuberculin-type allergy.

Bacterial Anaphylaxis. In Zinsser's[6] study, just referred to, he separated two antigenic fractions from the tubercle bacillus, a nucleoprotein and a "residue antigen."

With the former, the *nucleoprotein* fraction, anaphylactic sensitization can be produced just as with non-bacterial protein substances as heterologous serums or egg albumen. The incubation period is similar; the antibodies—precipitins, muscle- and skin-sensitizing—are the same; hence shock and passive sensitization may be obtained. The reactions are all of the immediate edema-hyperemia (wheal) type. This nucleoprotein also gives a tuberculin type of reaction in the tuberculous animal, but in its pure filtered form does not create sensitivity to tuberculin. However, crude (unfiltered) nucleoprotein may at times produce a mild sensitivity.

The "residue antigen" was described as a thermostabile, non-coagulable, non-dialyzable, non-protein material analogous to that recovered by Pick[7] (1912) from typhoid bacilli, and by Dochez and Avery[8] (1917) from urine of patients with pneumonia. In its crude form this "residue antigen" of Zinsser does not sensitize but gives a delayed tuberculin reaction in tuberculous animals. Zinsser and Parker[9] (1923) found chemically similar substances in all other bacteria investigated. Heidelberger and Avery[10] (1923) eventually purified a like substance from the pneumococcus and identified it as a carbohydrate type-specific substance. It is non-antigenic in that it cannot produce the antibodies with which it reacts. Enders,[11] using a purified carbohydrate specific substance of the tubercle bacillus, could elicit shock and contraction of uterine muscle (Dale reaction) in guinea pigs actively or passively sensitized to this bacillus. The polysaccharide or soluble specific substance is common to most bacteria, but it is particularly important in the pneumococcus group because it establishes type specificity. In other words, there is a different carbohydrate substance for each pneumococcus type, and specificity is determined by the molecular configuration of the carbohydrate radical alone. Substantiating evidence of the importance of a carbohydrate radical in an antigen was provided by Avery[12] and his associates (Goebel and Tillett)[13] who produced entirely new antigens with new specificities by means of synthetic sugar-proteins. The proof that molecular configuration determines specificity for antigens was thus established.

The polysaccharide fraction of the molecule, though non-antigenic, precipitates antipneumococcus serum, produces shock in sensitized animals, and gives an immediate urticarial reaction in pneumonia convalescents (Tillett and Francis[14]). All of these reactions are strictly specific.

Interesting as this phenomenon may be experimentally, bacterial anaphylaxis, which excludes the tuberculin-type allergy, plays little if any significant role so far as is now known in the pathogenesis or symptomatology of infectious disease in man. This knowledge has been useful in the diagnosis of the type of organism in pneumococcus pneumonia, but with the antibiotics now in use such information is rarely required.

The Tuberculin-Type Allergy. As previously mentioned, this is the type of response observed by Koch[1] in his tuberculous animals and was differentiated from bacterial anaphylaxis as a result of the work of Baldwin,[5] Zinsser[6] and others. A capacity to stimulate the tuberculin-type allergy is common to all bacteria. It develops rapidly and readily in all animals in eight to fourteen days after the injection of or invasion by living organisms, is specific, and is indicated by a delayed (twenty-four to forty-eight hours) inflammatory response to a skin test with bacterial substance.

The Active Production of Tuberculin-Type Allergy. For a long time experimenters failed to produce this type of allergy except by the injection of living bacteria which created actual disease. Since most of the work has been done with the tubercle bacillus, this organism will be discussed, but what holds for it is equally applicable to all bacteria, with minor exceptions. The principles are the same. Koch[1] showed that tuberculous animals not only gave a delayed skin test reaction but were killed by the injection of tuberculin in doses innocuous to normal animals. Baldwin[5] could not produce tuberculin reactions without actual infection, but Zinsser and Petroff[15] were finally able to get positive results after the intraperitoneal injection of very large amounts of dead bacilli. In 1934 Couland,[16] by incorporating heat-killed tubercle bacilli in solid paraffin, very easily produced tuberculin sensitivity of high degree and permanency in rabbits. Saenz,[17] and later Freund et al.,[18] obtained similar results, substituting liquid for solid paraffin. Using this method Casals and Freund[19] showed that the rhesus monkey, a very resistant animal, responded as well as rabbits. Freund et al.[20] demonstrated also the synergistic effect of this oil upon antibody formation.

Thus the *active* production of tuberculin sensitivity has been accomplished in normal animals in the absence of tuberculosis or tubercle, and in the absence of any suppuration or necrosis in the tissues, by the injection of dead bacilli incorporated in paraffin or paraffin oil. It takes eight to ten days to develop active sensitivity.

The Passive Production of Tuberculin-Type Allergy. Along with the experiments on active sensitization there were many workers who attempted, but failed, to transfer the sensitization to normal animals. This had been readily done with the anaphylactic type of sensitization. However, there is on record an early experiment of Bail[21] (1909), who injected an emulsion of tuberculous tissue into normal guinea pigs and twenty-four hours later secured a tuberculin reaction and death of the animals after a small intraperitoneal injection of tuberculin. Helmholtz[22] inoculated normal animals with defibrinated blood from tuberculous animals and reported tuberculin reactions in two to six days. McJunkin[23] used a filtrate of peritoneal exudate of animals with tuberculous peritonitis, injecting it into normal animals which became reactive to tuberculin but only after six to eight days. Unquestionably this must be interpreted as active, not passive, sensitization. Lange[24] reported on the use of filtered extracts of tuberculous tissue and demonstrated a tuberculin reaction in eight to ten days. As controls she used similar extracts of non-tuberculous tissue irritated by kieselguhr, i.e., a sterile inflammation, and the animals so injected likewise gave a positive reaction to tuberculin. The same criticism which applies to McJunkin's work[23] must obtain for Lange's[24] results, except that there is no explanation for the reaction in control animals injected with kieselguhr abscess extracts. These animals must have been accidentally infected. Zinsser and Mueller[25] used serum of tuberculous animals for passive transfer but regarded their results as very unconvincing.

The net result of these observations clarified the picture and finally the consensus of opinion is that a sensitization of the tuberculin type is strictly cellular, for it has not been passively transferred by serum or filtered fluids. But Bail's[21] and Helmholtz's[22] results after the injection of cells in tissue emulsion and defibrinated blood respectively take on significance in the light of newer work and the *short incubation period for the development of the sensitivity* they reported. Rich and Lewis[26] showed by tissue cultures that tissue cells from the allergic tuberculous body were highly susceptible to and were killed by tuberculin in amounts that did not damage the cells of tissues from non-tuberculous animals.

That the tuberculin antibody is cellular and that it may be transferred by cells, not by serum or cell-free exudates, has now been shown by Chase.[27] In his experiments, an extension of his work with Landsteiner,[28] guinea pigs were first rendered sensitive to tuberculin by a method similar to that of Saenz[17] and of Freund.[18] The cells from an artificially stimulated peritoneal exudate, from the spleen and from lymph nodes, were taken from these sensitized animals and after being carefully washed were injected into normal guinea pigs. By this method Chase obtained sensitization to tuberculin in sixteen of seventeen experiments in two to three days after an intraperitoneal implantation, and in twenty to thirty-six hours after intravenous injection. The intensity of sensitizations thus transferred varied with the number of sensitized cells injected and the degree of sensitivity of the cell donors. The serum of the cell donors did not transfer the sensitization.

The mechanism of production of tuberculin-type sensitivity still remains in doubt. It is a regular and specific cellular response to the infection with its attendant inflammatory reaction. Dead bacilli injected in large or in small amounts, with paraffin, paraffin oil, or agar, also stimulate it. In other words, an inflammatory reaction is necessary for the active stimulation of the specific cellular antibodies, as indicated in the experiments mentioned. The only experiments showing active sensitization without tubercles or inflammation are those of McJunkin[23] and of Lange,[24] who used the filtered peritoneal exudate of guinea pigs with tuberculous peritonitis and obtained a tuberculin reaction after six to eight days. This work has been confirmed, but as Zinsser[29] says "is not easy to repeat and has often failed in our hands but cannot be neglected in a discussion of the reaction."

Summary. There are two types of allergic response on the part of the body to bacteria and their products: (1) the anaphylactic, which is comparable in all respects to the non-bacterial protein sensitization. It is a protein reaction of the immediate edema-hyperemia (wheal) type. (2) Tuberculin-type allergy. This may be caused by any bacterial organism and specific evidence is obtained by a delayed inflammatory reaction, not a wheal. Inflammatory reactions of the body are necessary for its formation. The antibodies are cellular, not humoral; passive sensitization has been accomplished by Chase[27] with sensitized cells.

Relation of Bacterial Allergy to Immunity

Following bacterial invasion the body seeks to protect itself against bacterial substances by the production of antibodies. The bacterial substances chemically are proteins including endo- and exotoxins, cell-body proteins and other nitrogenous products, as well as carbohydrates and carbohydrate lipoids. The immune antibodies, so-called, include agglutinins, precipitins, alexins, opsonins, the antitoxins and others.

known but not named, such as the mouse protective antibody against typhoid studied by Longfellow and Luippold.[39] In addition to all these and in response to bacterial protein substances there are created important antibodies concerned with bacterial allergy of the tuberculin type, and the question arises as to their significance in relation to immunity— are they beneficial and protective, or are they harmful?

The general idea seems to have been that allergy is a phase in the direction of immunity, and the greater the sensitivity the higher the immunity. This is a concept taken directly from protein anaphylaxis on the basis of much early work indicating that sufficient humoral anaphylactic antibody protected the sensitized cell against the antigen. Krause[30] was one of many exponents of the immunity value of bacterial allergy in tuberculosis. More recently this theory has been questioned, and Rich[31] and his associates have contributed experimental evidence indicating a lack of relationship between immunity and allergy. In experimental syphilis they proved that immunity existed without any allergy. In other experiments, Rich with Brown[32] showed "that the immunity of allergic, immune animals could be passively transferred to normal animals without the concomitant transference of hypersensitivity"; and with Jennings and Downing[33] he showed that in the allergic, immune animal (pneumococcus and Pasteurella infection) the sensitive (allergic) state could be removed without a corresponding loss in the immunity. Rich[34] thus sums up his conception of the harmfulness of bacterial allergy as opposed to the value of immunity as follows: "In a very realistic sense it may be said that the presence of allergy converts, in effect, a bacterium which does not produce a toxin into one that does, i.e., it converts the harmless protein product of bacterial disintegration into a violent and even lethal poison......in spite of the widespread and dogmatic assertions about the protective role of allergy, there is not one single experiment or observation on record through which hypersensitiveness has been shown to be necessary for the operation of immunity in any infection under any condition whatsoever."

Topley and Wilson[35] in their discussion of this theory do not agree, for they say, "we believe that the experimental and field evidence suggest that allergy is a step on the road to immunity. Though, in general, allergic subjects will be found less liable to develop clinical tuberculosis than those who have never been in contact with the tubercle bacillus, there are large numbers of exceptions." In spite of this opinion Topley and Wilson present three different observations on the relation of tuberculin allergy, as expressed by a positive tuberculin reaction, to active tuberculosis: (1) that of Heimbeck[36] which shows that "the incidence of tuberculosis was over seven times as high in the positive as in the negative group" among nurses exposed to tuberculosis patients. (2) That of Shipman and Davis[37] who, in their study of nurses, report that the proportion of nurses developing tuberculosis was higher in those tuberculin-positive than in those who were tuberculin-negative. (3) Figures on nearly 100,000 South African gold miners showed an incidence of clinical tuberculosis of 3.47 per 1000 in tuberculin-negative workers, and 6.83 in the weakly or moderately positive group, and 15.5 in the strong reactors.[38]

Such data would seem to indicate that the greater the sensitivity the greater the susceptibility; certainly immunity is not indicated.

The probability is that such data indicate nothing from the standpoint of immunity, using the word in the sense of protection against disease, the reason being that the tuberculin test is only an indication of sensitization from past and conquered or existing infection, for how else can one explain the high percentage (84.5) of the strongly reacting mine laborers who had no clinical tuberculosis. What is needed is a *protective titre test* such as that for the pneumococcus and that developed by Longfellow and Luippold[39] for the typhoid bacillus. A comparison of such a test with the tuberculin test would probably show that the latter is only an indication of an immunologic sensitized state and not a measure of immunity, meaning resistance and protection, and that the two cannot be related.

Mackenzie,[40] in a study of anaphylaxis (immediate reaction) in pneumococcus immunity, concludes, "it appears to be a concomitant without any significant role in the immunity mechanism." Clawson,[41] using streptococci, was able to separate allergy from resistance (immunity) and he concluded from his experiments that allergy bears no relation to general resistance, and that it seems to be a useless and at times harmful concomitant phenomenon.

Summary. Present-day opinion on bacterial allergy and immunity tends to favor the idea that they are not parts of the same process of protection. They may exist together or separately. Immunity is a protective process while allergy is an inflammatory and necrotic process which is essentially harmful.

Allergy in the Infective Diseases of Man

The Streptococcus Infections. Acute infections with the proper types of streptococcus may give rise to scarlet fever, erysipelas, tonsillitis, rheumatic fever and many other clinical diseases. Regarding solely the sensitization aspects, good evidence has been produced experimentally and clinically which indicates allergy is an important factor in the pathogenesis of diseases due to streptococcus. There have been many important contributions by many workers which may be summed up as follows.

In *scarlet fever*, Bristol's[42] suggestion that the rash is an allergic phenomenon has been supported by Dochez and Stevens,[43] who found that newborn infants, in contrast to adults, did not react to the filtrates of broth cultures of scarlatinal streptococci, and J. Cooke[44] showed that the blood serum of newborn babies had no neutralizing capacity. In other words, they simply had not yet become allergic. But sensitization is early established through the chance bacterial invasion of the throat which so frequently occurs.

Erysipelas has been studied from the viewpoint of allergy, particularly by Birkhaug,[45] and his conclusions that it is a sensitization reaction to Streptococcus erysipelatis support and are supported by the work done with streptococci in scarlet fever.

Rheumatic fever as a phenomenon of bacterial allergy has received support from Swift[46, 47] and from Coburn.[48] This disease has one of the most varied and widespread pathologies, involving joints, muscles, nerve tissue and viscera. Swift's[47] arguments have been based mainly on analogies between rheumatic fever and tuberculosis and syphilis. He and his associates[49, 50, 51] found experimentally that focal lesions were necessary to incite the allergic state, which could then be maintained by small doses of non-hemolytic streptococci that had no effect on non-allergic rabbits. One of the significant conclusions from the study of rheumatic fever is that there is no specific agent nor even a particular strain of streptococci that plays an etiologic role. This, according to Swift,[49] supports the allergy theory for it explains how many different types of streptococci may all induce the same clinical and pathologic disease, a feature which is quite common to all allergy. Rich[52] arrived at the same conclusion regarding rheumatic fever as a manifestation of allergy from a pathologic-anatomic point of view on account of the similarity of the rheumatic fever lesions to those he describes in patients after serum and egg allergy, namely focal collagen alteration, "the Aschoff bodies," the focal lesions in the heart muscle, the verrucose valvular lesions, and the blood eosinophilia.

Tuberculosis. As has been said, hypersensitiveness in tuberculosis is indicated by the unusual degree and accelerated response to tuberculin in doses innocuous to the non-tuberculous. The tuberculin skin test is an indication of this allergy to tuberculoprotein which, purely as a result of the sensitization of the host, has become an active necrotizing poison.

Syphilis. Noguchi[53] used emulsions of killed Treponema pallidum to produce allergy to the organism and introduced the luetin test, a tuberculin-type test reaction, as an indicator. Sensitivity becomes well established in the tertiary stage when the reaction is characterized by the destructive inflammatory tissue changes. The luetin skin test, however, is not accepted today as a standard diagnostic procedure.

Pneumococcal Pneumonia. Tillett and Francis[54] reported the immediate urticarial reaction to the type-specific carbohydrate substance at the close of the active disease and the tuberculin-type of response on skin test to the protein fraction which is not type-specific. These findings were confirmed by Finland and Sutliff.[55] Francis[56] later observed that the positive urticarial reaction indicated a good prognosis and its absence a fatal one. The point is that the positive skin test is possible and obtained only when there is adequate specific antibody in the blood to overcome the infection. In this case an allergy of the immediate type is favorable to the patient, and this is about the only instance in which this is true. Finland and Dowling,[57] using the polysaccharide by intradermal injection, induced a skin sensitivity and the specific antibodies also appeared in the blood; in short, they induced an active immunity. The introduction of the antibiotics at this time undoubtedly interrupted studies which would have added to our further knowledge of allergy and immunity in pneumococcus infection. What is said here applies equally well to the type-specific substance and antibody of the meningococcus.

The Allergic Diseases. In addition to the allergies which are merely a part of clinical disease due to specific and infecting organisms, there are the accepted diseases in which the allergy feature dominates the picture. In Chapter 7 there has been extensive discussion of the importance of infection and its causal relation to asthma; and likewise in the chapters on hyperplastic rhinitis, allergic dermatitis, and the various dermatoses, and on allergy in neurology, in gastro-intestinal and in ophthalmic allergy.

In all of the chapters dealing with allergy of the various systems, evidence has been given that bacteria may be etiologically concerned in the production of the allergic manifestation. The belief that infection is a cause is based on the history of antecedent and concomitant infection, the reproduction of the signs and symptoms, or their relief by removal of foci or by treatment directed against the bacterial agents.

If one takes a broad view of the entire field of the allergic diseases so-called, it would appear that with our present limited knowledge and as we understand it today, the majority of the clinical evidences of bacterial allergy belong in that group we have designated as the *tuberculin type*. The reason for this is a rather negative one, namely patients with bacterial allergy, with rare exceptions, do not react by immediate wheal reactions on test with bacterial filtrates or heat-killed vaccines.

On the other hand, diagnostic skin tests for reactions of the tuberculin type have proven unsatisfactory for the reason just stated, namely, using preparations of the ordinary pathogens, as the pneumococcus or streptococcus group, positive reactions are obtained which may indicate nothing more than a past infection and not an existing active one. The symptomatic reaction is the only clinical proof available today as a fairly conclusive index of a cause, providing it is obtained with an autogenous vaccine.

It may well be that the bacterial test materials for clinical use have not been correct or adequate, for little or nothing has been done in this field using such knowledge as we already have with substances obtained from bacteria, as carbohydrates, protein, or even carbohydrate lipoid. The subject deserves comprehensive study because of its importance.

In the diseases of allergy (asthma, rhinitis, urticaria, eczema) there appear to be three types of tissue response to bacterial products that have their counterparts in reactions to non-bacterial products, namely (1) edema-hyperemia, (2) the inflammatory, and what, for lack of a better word, I shall speak of as (3) the dermatitic (eczematous). These in general are indicated by the immediate skin test wheal, the delayed inflammatory (tuberculin-type) reaction, and the delayed exudative type of response to patch test which has not as yet been actually demonstrated in spite of the highly suggestive evidence presented (Chapter 14) that bacterial products produce eczematous lesions.

Skin Tests in the Diagnosis of Bacterial Allergy

These may be divided into the tests for immediate wheal reactions, and for the delayed tuberculin-type response.

1. Immediate Urticarial Reactions. Skin tests, upon which dependence may be placed, with reservations, for inhalant and food allergens, play a very subordinate role in bacterial allergy. The immediate wheal reaction, occasionally with resulting systemic effects, may be obtained with the soluble specific substances of the pneumococcus and the meningococcus. An asthmatic patient of mine with a long standing chronic infection with pneumococcus Type XXIX had a marked immediate local skin reaction with edema of both eyes after the injection of 0.1 ml. of a 0.01 per cent per volume heat-killed vaccine of this organism. Occasionally such reactions are obtained with diphtheria and tetanus toxins. Anaphylaxis to toxins was noted in animals by von Behring,[58] by Knorr[59] and others. It was observed and studied by Neill[60] and his associates in a patient giving an immediate wheal reaction on Schick test. This was found to be due to a constituent of the diphtheria bacillus. Hooker[61] has observed a similar reaction. Another one of my patients, B. P., aged one year, an asthmatic infant with allergic dermatitis, had an immediate local and constitutional reaction with asthma and general urticaria one hour after a dose of 0.5 ml. of diphtheria toxoid.

Occasionally one gets an immediate urticarial wheal with such fungus preparations as trichophytin or oidiomycin. Systemic reactions (asthma and urticaria) have been recorded following intradermal tests with such solutions.

Other immediate reactions that may have diagnostic significance are also observed in connection with such parasites as echinococcus, trichinella, filaria and schistosoma.

The immediate reactions to tetanus toxoid are well recognized. In a study by Cooke et al.[62] it was determined that this is a reaction not to

Clostridium tetani but to the proteose substance in the culture medium, hence not a bacterial allergy.

2. Delayed Tuberculin-Type Reactions. This inflammatory reaction is the commonest type of allergy to bacterial substance. The tests are useful in diagnosis only under special conditions in certain diseases. The difficulty is that they do not distinguish between present and past disease. A list of those diseases in which the tuberculin-type reactions may be used diagnostically is as follows:

Tuberculosis
Typhoid fever
Brucellosis
Tularemia
Glanders
Lymphogranulomatosis inguinalis
Dermatophytosis
Leishmaniasis

Even with the specific test materials for these diseases a positive test does not indicate existing and active infection. Clinical study and diagnostic acumen are required for proper interpretation and evaluation. Neither should these allergic reactions, if obtained, be interpreted as an indication of resistance. The existence of allergy does not mean immunity (protection). The required technics for these tests may be found in special treatises on clinical and laboratory procedures.

In general, in allergic diseases such as asthma, rhinitis and the edemas, due to chronic focal infection, skin tests with vaccines either stock or autogenous are practically useless. In a small, carefully observed group of cases of infective asthma which I reported in 1934,[63] seventy patients were skin-tested with 0.1 ml. of an 0.1 per cent per volume autogenous heat-killed vaccine. Nineteen had symptomatic asthma and a delayed skin reaction after twenty-four hours. Eight others with symptomatic asthma had negative skin tests. On the other hand there were thirty-two others with no symptomatic reaction of asthma, but twenty-five of them gave positive skin tests.

It is not possible today to attach any significance to the delayed skin reaction to bacterial tests as a method of etiologic diagnosis for such diseases as asthma, hay fever, urticaria, and the like. The uselessness of such tests with derivatives of hemolytic and non-hemolytic streptococci was brought out by Mackenzie and Hanger,[64] who found the test reaction to be positive in a very large percentage of adults. While the reaction probably indicates allergy due to previous and minor contacts there is no way of differentiating the allergy of existing infection from that acquired in the past.

3. Delayed Dermatitic Reaction. Patch testing with bacterial substances or products has not yet elicited a local exudative reaction characteristic of dermatitis. Since an injection of autogenous vaccine has produced the symptomatic response, that is, a clinical exacerbation of dermatitis, patch testing with bacterial substances as a diagnostic procedure is a not improbable future development.

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27. *Inhalants*

(*Air-borne Allergens*)

ROBERT CHOBOT

AIR-BORNE allergens have clinical significance depending upon whether they are absorbed by the mucous membranes (inhalants) or through the skin as external contactants (percutaneous absorption).

Mucous Membrane Absorption

Air-borne substances when inhaled show their effect primarily upon the nasal, pharyngeal, conjunctival and bronchial mucous membranes whenever sensitization exists. This explains why inhaled allergens are especially important in allergic rhinitis and asthma.

The immunologic mechanism through which they operate is the skin-sensitizing antibody cellularly attached to the cells of the mucous membrane as well as to the skin. The reaction therefore is of the "immediate" type with edema and hyperemia, and in general those substances inducing the positive immediate wheal test in the skin are reactive also in the mucous membrane. To this there are of course the many exceptions noted in the chapter on skin testing, for it does not follow that even if the skin test is genuinely positive the mucous membrane will be sensitive also.

Recently Johnson and Alexander[1] have brought evidence, by immunologic technics, in their studies on hay fever due to ragweed that there is ragweed antigen circulating in the blood of normal persons as well as those with hay fever. If ragweed antigen is circulating in the blood of specifically sensitive individuals it is difficult to understand why it does not react with the demonstrable antibody cellularly attached to the skin and give rise to general urticaria as a part of the symptom complex of hay fever. One explanation may be that the ragweed antigen has become denatured in so far as its specificity for the skin-sensitizing antibody is concerned while its specificity for the anti-ragweed rabbit antibody used in their experiment remains intact. This is a most interesting observation, the complexities of which remain for future solution.

The fact is that air-borne substances when inhaled give rise to the immediate reaction in the mucous membranes specifically sensitive to them. Proven cases of the delayed type (over one hour) of reaction have not as yet been recognized, nor is it recognized that air-borne substances can give rise to other systemic reactions, for instance, gastro-intestinal, in the absence of coryzal or bronchial symptoms.

Percutaneous Absorption

The natural protective and absorptive capacity of the unbroken skin prevents cutaneous reactions against most allergens constantly present in the air. Occasionally though rarely, intimate and prolonged contact with an air-borne allergen may give a localized urticarial wheal though this is of no clinical significance and is in the nature of a positive skin test of the immediate type.

Air-borne substances may, however, give rise on occasion to the dermatitic type of allergic reaction. This is a "delayed" exudative reaction and is seen clinically in the few reported cases of seasonal allergic dermatitis due to pollens and that due to the resins of poison ivy and sumac in the smoke of burning brush.

The Air-borne Allergens

The allergens air-borne and acting by inhalation are usefully classified as:

1. **Pollens.** These are the chief cause of seasonal hay fever and asthma. They are not causes of vernal catarrh though they may be complicating factors (see Chapter 24). One case of seasonal somnolence presumably due to ragweed is cited by Sternberg.[2] On oral therapy for hay fever pollens are known to cause acute gastro-intestinal symptoms. In all these instances they act as allergens giving the immediate skin reaction of the wheal type.

There are a few instances in which pollens have given the delayed dermatitic skin reaction either to the alcohol-soluble phenols or to the protein fraction.[3, 4, 5]

2. **Animal Emanations.** The allergens of animal origin consist of the danders, not the insoluble hair, and equally important though not always appreciated is the saliva which, licked onto the animal's coat, dries and scales off to become an active allergen in the dust of the home. These substances also act to give rise to the immediate wheal type of allergy. (See Non-infective Asthma, Chapter 6, and Perennial Rhinitis. Chapter 12.

3. **Volatile Substances.** That volatile oil may give rise to typical allergies, especially asthma, is well recognized (Chapter 6, p. 108), but the cases are not common and the proof that they are antigen-antibody reactions is not well established in many instances. A curious case of syncope was cited in Chapter 19, (p. 333). It is well recognized that many of the exquisitely fish-sensitive patients will develop severe and prompt asthma from fish being cooked in the kitchen or even from fish in the market. Since these patients give a wheal reaction of the immediate type

to the heat-stabile nitrogenous molecule of fish glue, it must be that this component is carried in sufficient amounts in the moisture of the air.

Dermatitis reactions to volatilized chemicals as formalin are well recognized and are regarded as allergies. The number of known substances operating in this way is very limited.

4. Vegetable Substances. These constitute an important group which includes the cosmetic powders and lotions, for it must be remembered that the latter when dry leave behind the materials carried in the solution, as for example, the flax seed in certain hair-set lotions. (See Chapter 12, Vasomotor Rhinitis.)

Castor bean dust[6, 7] is an extremely potent allergen in producing asthma and rhinitis. Sensitivity is seen in those handling the beans, those who work in the mills and those who live within a mile of the places where the pumice is being prepared. This pumice or flour from the castor bean has been used, after the oil has been extracted, as an organic high-nitrogen fertilizer. It must therefore be kept in mind as one of the important air-borne allergens of vegetable origin in certain limited regions.

(*a*) *House dust* is probably the most important single air-borne antigen for asthma and rhinitis. No one has yet discovered just what it is or from what it is derived. Though it may contain many allergens from the home, as danders, feathers, orris, etc., it still has a specificity of its own.[8, 9, 10] It is possibly a derived or split molecule from one or several other substances, but its molecular instability renders chemical purification and analysis extremely difficult and is the reason for our continuing lack of information.

(*b*) *Food Substances.* Many of the flours of cereal grains and seeds when carried in the air cause symptoms of rhinitis and asthma. The inhalation of these vegetable dusts is met with among bakers, millers, farmers and by cooks and housewives in their duties in the home. When air-borne, these substances are as highly active as pollens with a sensitization of the immediate wheal type.

It is a fact that many patients reactive by skin test to the extracts of wheat develop clinical symptoms only when wheat flour is inhaled. They eat it with impunity. If this fact were more widely recognized, if patients reacting to wheat extract were put on more stringent therapeutic trial, there would be less demand for wheat-free diets than now exists. Every case reactive to these cereal flours should be made to prove the existence of a clinical allergy to the flour when eaten, bearing in mind that the symptomatic response should be definite on three successive trials at the same time interval under identical conditions.

(*c*) *Molds.* These constitute an important factor in asthma and hay fever. The air-borne spores have a certain seasonal and geographic variation, but spores do exist within the home to a limited extent throughout the year. Like the pollens, they exert their effect as allergens through the mechanism of the immediate wheal type of sensitization. As a rule they are not very active antigens.

Since van Leeuwen's[11] original observations on this subject in 1924 in Holland, there have been many reports in the literature. In America, Cadham[12] in 1924 was the first to cite a case of asthma due to fungi (wheat rust). Hopkins, Benham and Kestin[13] reported asthma from Alternaria spores and reported positive cutaneous reactions and positive passive transfer tests in a case of eczema due to Alternaria. They also produced an attack of asthma by means of a nasal spray with Alternaria extract. Bernton and Thom[14] reported a case of asthma due to Cladosporium. Flood[15] tested fifty-five patients by the scratch method and found eight reactors. In one patient he succeeded in precipitating an attack of asthma by spraying the throat with a broth filtrate of Mucor plumbeus. Jiminez-Diaz[16] and co-workers in 1932, using Mucor, Penicillium and Aspergillus, produced asthma by spraying a pillow with Penicillium extract. They found fourteen marked skin reactions in seventeen patients tested, and the serum of three reacted by passive transfer test. Towey, Sweaney and Huron[17] reported a group of patients sensitive to maple dust, which on culturing was found to contain Conidiosporium corticola. Their patients had positive scratch tests, negative transfer tests, and did well on environmental removal.

INCIDENCE OF POSITIVE SKIN REACTIONS TO MOLD EXTRACT. Some work has been done on the incidence of reactions to fungus extracts. Balyeat[18] in 1932, in Oklahoma, found that only 1 per cent of the 408 patients tested reacted to common fungi, and only two patients were clinically sensitive. On the other hand, Feinberg[19] in Chicago found 28 per cent reactors on scratch tests in 243 patients tested. Lamson and Rogers[20] in 1936, in Los Angeles, tested 1259 patients and found 154, or 12 per cent, reacted to one or more molds by intracutaneous test. Alternaria was found to be the most common allergen. No positive transfer tests were performed. Brown[21] noted that of twenty-four patients tested there were twelve reactors to Alternaria. Schonwald,[22] in the Pacific Northwest, tested 150 selected patients who had a possible mold sensitivity. He found 145 reactors, or 76 per cent. Fraenkel[23] in 1938 found 53 per cent positive skin tests to molds in 185 asthmatic patients tested in England, and 15 per cent reactors in 522 cases tested in Germany. He believed the difference in incidence of positive tests was due to the difference in climate.

Feinberg and Little[24] gave evidence borne out by scratch tests, mold spore counts, clinical history and therapeutic trial for the importance of Alternaria sensitivity, particularly in seasonal hay fever and asthma. Feinberg used any or all of the following selected groups in whom he suspected mold sensitivity: (1) patients with a poor response to pollen therapy; (2) patients whose symptoms did not fit in with any known pollen season; (3) patients with an indefinite history of onset or cessation of their pollen symptoms; (4) patients who had negative skin tests to pollen and seasonal symptoms. He found, in his series, positive skin tests by the scratch method, and an occasional positive passive transfer test. Most of his patients had an exacerbation coincident with the increase in spore counts.

The work has been corroborated by Pratt,[25] in Boston, in a large series of allergic children. In 1938, reporting on twenty-six Alternaria-sensitive patients tested with undiluted extracts of unknown strength he found that twenty-four gave a positive reaction, an incidence of 92 per cent. In the other fungi studies (Aspergillus, Hormodendrum and Penicillium), there were ten positive reactions in twenty-four patients tested. Atmospheric mold spore counts have been reported by Feinberg, Durham and Pratt.

Together with Dundy and Schaeffer, Chobot[26] studied 123 children and 117 adults. They were all allergic to inhalant substances and were tested routinely to the following molds: Alternaria, Aspergillus, Hormodendrum, Penicillium, Mucor and yeast. Intracutaneous tests were done with extracts of 100 and 1000 protein nitrogen units. Twenty-eight selected patients giving marked positive cutaneous tests were tested ophthalmically with extracts of 5000 unit strength.

We concerned ourselves, in this study, chiefly with Alternaria and the number of reactions to it. In a series of 240 patients suffering from inhalant allergy, thirty patients gave marked skin reactions to Alternaria extract in dilutions of either 100 or 1000 protein nitrogen units, and thirty-six gave moderate reactions. On a percentage basis, 27.5 per cent gave moderate or marked reactions on intracutaneous testing. However, only 12.5 per cent gave really marked cutaneous reactions. Aspergillus gave marked skin reactions in three cases (1.2 per cent) and moderate reactions in twenty-three cases (9.6 per cent). Mucor reactions were marked in three, and moderate in three (2.1 per cent). Penicillium gave marked reactions in ten cases (4.2 per cent), and moderate in seventeen (7.2 per cent). Yeast reactions were marked in four (1.9 per cent) and moderate in sixteen (7.6 per cent).

Of the 240 patients tested, twenty-five (10 per cent) gave reactions to other molds as well as a positive reaction to Alternaria. The incidence of positive cutaneous tests to molds in children and adults is shown in Table 30. It is noticeable that in this group the number of marked reactions to Alternaria was the same in children and adults, namely 12 per cent.

A selected group of twenty-eight patients giving moderate or marked positive skin reactions to Alternaria extract were tested ophthalmically with 5000 units of this extract and passive transfer studies were also done. Out of this series of twenty-eight, eighteen gave positive transfer tests, and twelve had positive eye tests. That is, twelve out of the 240 patients had mucous membrane sensitivity to Alternaria. When the eye tests were positive the indirect or transfer test was always positive, but in six cases skin-sensitizing antibodies were demonstrable without positive eye tests.

Insufflation was done with Alternaria spores. It was found that inhalation, with plates containing pure cultures of Alternaria placed beneath the patient's nose, caused no reaction. However, when spores were placed on an applicator and applied to the turbinates a positive nasal response with edema and sneezing was elicited in all patients with a positive eye test.

NEUTRALIZATION TEST. Serum was taken from six Alternaria-sensitive patients with positive skin, eye and insufflation tests. Quantitative neutralization of Alternaria-sensitive serums was carried out to determine the relative neutralization capacity of Alternaria extract. The technic was that outlined by Cooke and his co-workers.[27] The serums were mixed with equal parts of Alternaria extract, varying in strength, in sterile tubes, and were placed overnight in the icebox. Intradermal skin sites, each containing 0.05 ml. of such mixtures, were then made in non-sensitive subjects. After forty-eight hours, when all reactions or irritations had subsided, the sites were tested with 0.025 ml. of Alternaria extract containing 17,000 units per cubic centimeter. The neutralization is shown in Table 31, and it occurs in mixtures of 5000 units or more. One serum, sensitive to Alternaria, timothy and ragweed, was mixed with 17,000 units of Alternaria. Sites were put in normal skin and then

TABLE 30

INCIDENCE OF MOLD REACTIONS IN ADULTS AND CHILDREN

Molds	*Total Tested*	*Number of Adults Tested*	*Number of Children Tested*	*Results*							
				Moderate Reactions				*Marked Reactions*			
				Adults		Children		Adults		Children	
				No.	%	No.	%	No.	%	No.	%
Alternaria	240	117	123	18	15.4	18	14.6	15	12.8	15	12.2
Penicillium	235	117	118	14	12.0	3	2.5	9	7.6	1	0.9
Hormodendrum	238	115	123	21	18.2	13	10.5	3	2.6	1	0.8
Mucor	140	48	92	2	4.3	1	1.1	3	6.3	0	0
Yeast	210	93	117	8	8.6	8	6.8	1	1.1	3	2.5
Aspergillus	240	117	123	16	13.6	7	5.7	3	2.5	0	0

Rearranged from data published in J. Allergy, *12*:46, 1940.

TABLE 31

NEUTRALIZATION OF SERUMS

Mixtures for Passive Transfer Sites	*Results of Tests 48 Hours Later**	*Mixtures for Passive Transfer Sites*	*Results of Tests 48 Hours Later**
Serum L mixed with		Serum We. mixed with	
Alternaria 100 Units	++++	Alternaria 100 Units	++
Alternaria 1000 Units	++++	Alternaria 1000 Units	++
Alternaria 5000 Units	++	Alternaria 5000 Units	0
Alternaria 17000 Units	0	Alternaria 17000 Units	0
Saline Control	++++	Saline Control	++++
Serum W mixed with		Serum Dit. mixed with	
Alternaria 100 Units	++	Alternaria 100 Units	++
Alternaria 1000 Units	+	Alternaria 1000 Units	++
Alternaria 5000 Units	0	Alternaria 5000 Units	0
Alternaria 17000 Units	0	Alternaria 17000 Units	0
Saline Control	+++	Saline Control	+++
Serum G mixed with		Serum Da. mixed with	
Alternaria 100 Units	++++	Alternaria 100 Units	+++
Alternaria 1000 Units	+++	Alternaria 1000 Units	++
Alternaria 5000 Units	++	Alternaria 5000 Units	0
Alternaria 17000 Units	+	Alternaria 17000 Units	0
Saline Control	+++	Saline Control	+++

* Passive transfer test sites were made by injecting 0.05 ml. of the mixtures (equal parts of the various serums and Alternaria extract in the concentrations stated) into the skin of a non-sensitive test subject. The sites were tested forty-eight hours later with 0.05 ml. of Alternaria extract, 17,000 units. Control sites were made with serums and saline equal parts.

Units are expressed in protein nitrogen per milliliter. One unit equals 0.00001 mg. of phosphotungstic acid precipitable nitrogen per milliliter.

TABLE 32

CROSS NEUTRALIZATION

PATIENT L.

Mixtures for Passive Transfer Sites	*Tested 48 Hours Later With*	*Results*
Serum and Alternaria 17,000 Units	Alternaria 17,000 Units	0
Serum and Alternaria 17,000 Units	Ragweed 20,000 Units	++++
Serum and Alternaria 17,000 Units	Timothy 18,000 Units	+++
Serum and Ragweed 20,000 Units	Ragweed 20,000 Units	+
Serum and Ragweed 20,000 Units	Alternaria 17,000 Units	+++
Serum and Ragweed 20,000 Units	Timothy 18,000 Units	+++
Serum and Timothy 18,000 Units	Timothy 18,000 Units	0
Serum and Timothy 18,000 Units	Alternaria 17,000 Units	+++
Serum and Timothy 18,000 Units	Ragweed 20,000 Units	+++

The procedures are the same as those used in Table 31.

tested forty-eight hours later with the respective antigens as shown in Table 32. Alternaria neutralized only against itself, and not to timothy or ragweed; therefore it is a specific antigenic substance.

CLIMATIC AND GEOGRAPHIC VARIATION IN MOLD PRODUCTION. Prince[28] in 1934 demonstrated the importance of atmospheric mold spores in Texas, where wind direction was a factor. Patients experienced exacerbations of their asthma when the wind was from the direction of the swamps on the neighboring mainland. Contrary to the experience of others in the other parts of the country, he found (1937) Alternaria was not a factor. The peak for the fungus spores was in the winter months.

Durham[29] conducted a survey of the prevalence of Alternaria spores on pollen slides, exposed at forty weather bureau stations scattered over the United States. He found them varying in abundance in many parts of the country from May to November. Distribution was somewhat similar to that of ragweed, although it extended farther west toward the Rocky Mountain area, where the lessened rainfall is not as conducive to ragweed growth. Conversely, it was less abundant along the eastern seaboard. Durham remarked that the Alternaria belt corresponds roughly with the wheat or grain growing belts.

Durham[30] in 1938 described an unusual shower of Alternaria and Hormodendrum spores which occurred throughout the eastern part of the United States on October 6 and 7 in 1937. On those days there were rapidly moving air masses spreading east and southeastward. He concluded that the crop of spores originated in southern Minnesota. Within twenty-four hours they had been carried as far east as New York City and as far south as Oklahoma City. The spore yield on pollen slides at remote stations was one hundred times that of the mean daily count for the month exclusive of the day of the storm.

Air-borne fungus spores may cause seasonal conjunctivitis. Simon[31] reported on a patient reactive to Alternaria and Cladosporium extracts who had positive skin and conjunctival tests and was always relieved following the injection of the extract of both fungi.

Bernstein and Feinberg[32] in 1942 reported daily counts of the mold spores in the air covering a period of five years. Determinations were made by both microscopic examination using the same method as in pollen counting, and by making cultures on suitable media. They found the most frequent air-borne spores to be those already listed as causing the inhalant allergies, that is, Alternaria, Hormodendrum, Cladosporium, Penicillium, Aspergillus, Rhizopus, Mucor, Chaetomium, Monilia and Tortula. Others were encountered less frequently. They found, especially with Alternaria and Hormodendrum, the two fungi most intensively studied, that there is a distinct seasonal variation, the increase in Chicago starting in May, reaching a peak in September or October and returning to a low level in December and January. With pollens there is a period of low prevalence between the grass and weed seasons. This is not the case with fungi. They are increasingly prevalent in July and early August. This corresponded with clinical experience in that persons allergic to grasses and ragweed, who continued with symptoms between the two seasons, were often found to be allergic to Alternaria.

TREATMENT OF MOLD-SENSITIVE PATIENTS. Having established the importance of molds as a causative agent, treatment is carried out similarly to that of the pollen allergies by a dosage such as given in the following table:

PROPHYLACTIC TREATMENT WITH ALTERNARIA EXTRACT*
SCHEDULE OF AVERAGE DOSES

Mold Extract 1000 P.N. Units		*Mold Extract 10,000 P.N. Units*	
First Injection	0.05 ml.	After 1 week	0.1 ml.
After 1 week	0.1 ml.	" " "	0.15 ml.
" " "	0.2 ml.	" " "	0.2 ml.
" " "	0.4 ml.	" " "	0.25 ml.
" " "	0.7 ml.	" " "	0.3 ml.
		" " "	0.4 ml.
Then mold extract 10,000 Units.		Then 0.4 ml. every 2 to 4 weeks.	

* Extracts of other molds or a combination of molds may be used on this schedule if indicated.

Constitutional reactions may occasionally be seen in mold-sensitive cases just as in the cases of pollen sensitivity. I wish to emphasize, however, that a large number of the patients will give a moderate skin reaction which is not transferable and has no real significance. Treatment in these patients, as would be expected, is entirely unsatisfactory. The best criterion for treatment is the ophthalmic test (p. 463). If this is positive, treatment is indicated.

The results of the treatment are satisfactory and the addition of this type of inhalant therapy in the properly selected cases is important.

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28. Food Allergy

ROBERT CHOBOT

ALLERGY to ingested foods and gastro-intestinal allergy are not synonymous, for foods may cause any type of clinical reaction with or without any associated symptoms of the alimentary tract.

The incidence of food allergy is a much disputed question. Schloss[1] was among the earliest to describe in modern terms the sensitization of infants to foods, though the existence of this intolerance or idiosyncrasy as it was called has been well recognized for centuries by parents if not by physicians. Some observers, as Rowe[2] and Vaughan,[3] place the incidence very high (40 to 60 per cent of allergic patients). The majority of qualified students regard this as much too high and place it more nearly in the range of 5 to 10 per cent of allergic patients. The reasons for this discrepancy are: a too liberal interpretation of what constitutes a positive skin test; a misinterpretation of coincidences which are curiously common in medical practice; and the difficulty of established and proven diagnoses.

In infants, sensitization to foods is relatively high and ranks in importance with infection, while after five years the food sensitization tends to spontaneous disappearance, making the incidence of clinical food allergy low in relation to that caused by inhalant substances and infection.

The Immunology of Food Allergies

There are several different mechanisms involved in the response to food allergens.

1. *The immediate* (under one hour) *wheal type reaction* with positive direct and indirect (passive transfer) test is the most common. Walzer[4] has shown that ingested protein is readily absorbed through the intestinal mucosa in unaltered form, hence in specifically sensitized persons the clinical response is prompt and usually the symptoms of such acuity that there is no question as to cause and effect. These reactions are therefore known to the patient, and in infants to the mother, and are not often a diagnostic problem for the physician.

2. *Delayed reactions* (over one hour) of the edema type are in part explained as due to split products of ingested food. Certain of these have been shown[5, 6] to be due to proteose fractions which give positive direct and indirect wheal tests of the immediate type, the delay being due to the digestion to the proper antigenic stage. It is not known whether

this obtains for all delayed reactions, but probably not. However, delayed reactions of the tuberculin type for foods have not as yet been recognized.

3. *Dermatitic reactions* to foods which are also delayed are known to exist and have been discussed under Intrinsic Allergic Dermatitis (Chapter 14).

Etiology

It may properly be assumed that any food may cause a reaction in an individual case. The proteins of foods are the usual causes of the immediate and delayed edema reactions and particularly those foods taken in relatively uncooked state or those containing heat-stable proteins. For this reason milk, egg, fish and shell fish stand high on the list of such antigens.

In the dermatitic reactions the foods proven to be antigenic in a few cases in the Allergy Clinic at the Roosevelt Hospital are those of fruit and vegetable origin, possibly because of the high content of resinous material. There is not yet much information on this point, which is not in conformity with the ideas of most observers who believe that milk, eggs and wheat are the important agents (see Chapter 14). While proteins may give this type of exudative lesion it is more logical to believe that the agents are of the same chemical order—metals, phenols, dyes, etc.—as those giving the delayed exudative lesions on external contact, i.e., extrinsic allergic dermatitis.

Symptomatology

Acute general systemic reactions are relatively frequent in infants. In adults the possibilities for such allergies cannot be said to be rare as indicated by history but they are seldom medical problems for foods producing such reactions are scrupulously avoided.

The importance of foods in asthma, rhinitis, dermatitis, various neuropathies, as well as allergies of the eye and gastro-intestinal tract, have been discussed in the several chapters on the allergies of these various systems and need not be elaborated here, but any cell or tissue of any organ may react to one or another allergen dependent upon the immunologic mechanism and the capacity of the cell to respond.

Diagnosis

The very first step lies in determining whether or not the child or adult is allergic, and one of the factors that will aid the clinical diagnosis is a careful family history. Since allergy is a constitutional weakness with many hereditary factors, a positive family history is of great help. It is essential to attempt to ascertain the existence of other allergies in the patient. Care should be used in reviewing his medical history, past and present, with that view in mind. One of the characteristic observations, particularly in children, is the cyclic recurrence of these attacks. This makes these patients invalids until the cause of their trouble is ascertained.

Skin tests may be done if there is anything that suggests the immediate type of response. If all indications point toward a delayed mechanism I believe that complete skin testing is contraindicated. The absence of skin reactions in this group of cases is of no importance. These patients are as allergic as those giving marked immediate skin reactions. Blood eosinophilia should be looked for, and if present it lends support to the diagnosis of an allergic condition. In cases in which skin tests afford no information, one must resort to restricted diets, usually readily improvised, or one may use the elimination diets of Rowe.[7, 8]

The principles of diagnosis are those discussed in Chapter 2. In the allergic individual a reaction ensues whenever sufficient antigen is in contact with sensitized cells. This means that for certain substances, as casein, there may be a relatively high tolerance because of its slow absorption rate and low antigenicity, whereas rapidly diffusible egg white gives a reaction with relatively small amounts when the reacting cells lie outside the digestive tract.

Care should be taken to prove a clinical sensitivity to foods regularly eaten, as milk, egg, wheat, chocolate and fish, for restricted diets are unnatural and may lead to undernutrition and create psychic problems in children and adults as well. Non-essential foods may be avoided without difficulty for trial periods, but no patient should be made overly conscious of any dietetic restriction unless there is real necessity.

If a patient has strictly avoided a food for one to two weeks with continuing symptoms, and if that food is again eaten in quantity for four or five days without a decided exacerbation of the symptoms, such a food cannot be considered to be a causative factor.

Management of Food Allergy

There is no food that cannot be avoided entirely, but milk and egg are certainly the most difficult. I have never found it necessary to provide the elaborate menus frequently advised. A problem of recent years resulting from the war has been the use of substitutes and inadequate labeling of prepared and proprietary foods. This applies particularly to those in which the fat content is made up from peanut, coconut or cottonseed oil. For those very sensitive to these foods some reactions have resulted, but on the whole few, for the allergies are infrequent.

For those infants genuinely sensitive to cow's milk, modifications and substitutes are possible (see Chapter 25). For those sensitive to the whey fraction, human, goat or mare's milk may be satisfactory. In all large urban centers, goat's milk from tested (tuberculosis and brucellosis) herds is readily obtained. Evaporated but not dried or condensed milk may be used, or milk boiled in a double boiler for about six hours is sufficiently denatured to be used without difficulty.

For those sensitive to the casein fraction, milk substitutes[9] with a soy bean base are available* since casein is not denatured by prolonged heating.

In adults, milk sensitization is usually of moderate grade and some milk in well cooked form is tolerated to a point where restrictions are not difficult or embarrassing.

Milk is used in cooking and baking, in the preparation of custards, cream soups, sauce or fillings, cakes, cookies and breads, and is used also by confectioners in making candies and whipped cream substitutes. Milk appears commercially as condensed (sugar-sweetened milk from which a considerable portion of water has been removed at low temperatures); evaporated (heated to 240° F.); and powdered or dried (whole milk with water removed at low temperatures). The latter is used in considerable quantities by bakers and is a common constituent of prepared cake and pancake flours. Milk is the important ingredient in ice cream, and great quantities are utilized in the manufacture of milk chocolate. Buttermilk is used by bakers for making cakes, bread, scones and rice buns.

Egg sensitivity in the infant is readily managed by the mother; if it persists to childhood usually the child protects himself. In the rare case of immediate allergy that has persisted to adult life with two of my patients, no major difficulty was encountered through school or college up to the time they were taken into the armed forces and given typhus or yellow fever (chick embryo) protective vaccine with severe systemic reactions. Under certain conditions egg white may appear in the milk of nursing mothers, as Donnally[10] showed.

Eggs are found in the following foods:

Batters for French toast, griddle cakes, waffles, breads, mayonnaise, macaroons, meringues, muffins, pastries of various kinds, puddings, and sauces such as Hollandaise. Bakers also employ eggs for many purposes, some of which are the preparations of almond paste, meringue and royal icings. Eggs are further utilized as a clarifying agent for sugar, as a means for giving luster to conserve bonbons, and in the preparations of ice creams and ices. The better ice creams consist of sugar, butter or cream, eggs and milk, while the cheap ice creams contain only milk thickened with corn flour or gelatin ice cream powder, colored and flavored with essences. Ices, such as pineapple, raspberry and strawberry, are made by rubbing the fruit through a sieve, combining the pulp with a custard (usually made with eggs) and freezing the mixture. Water-ices consist of water flavored with fruit juices or their essences combined with white of egg, sugar and coloring matter.

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* Mull-Soy, Borden Company. Sobee, Mead Johnson & Co.

Eggs are further used in the preparation of fancy sausages, in the manufacture of beef juices, e. g. Puro (a commercial preparation containing meat juice enriched by the addition of egg white), and in baking powder. White of eggs is used as an egg wash to give a glazed appearance to bread crusts, and to make a protective air-tight casing about meat for preserving.

In cases of delayed allergy there is a reasonable tolerance that makes rigid restriction unnecessary. Milk- and egg-sensitive patients merely avoid taking milk or egg as such and foods that are essentally milk or egg.

In all cases requiring dieting, care must be taken to avoid protein, mineral and vitamin deficiency.[11]

Treatment by desensitization so-called, which really should be spoken of as immunization, is uncalled for and ineffective, for most infants undergo spontaneous cure by loss of sensitization. In adults avoidance is easily practiced when the cause is known. Oral therapy with drop-by-drop increases has never been proven to produce the tolerance attributed to it but which nature unaided will provide in practically 90 to 95 per cent of the cases.

Summary

1. Clinical food allergies are relatively uncommon, contrary to the usual belief.

2. Clinical allergies that are immediate (within one hour) following food ingestion may be verified by the immediate skin test. Patients recognize these allergies so they are not diagnostic problems.

3. The delayed food allergies are difficult to diagnose for skin tests are negative to the allergens as eaten. As a rule they are determined by therapeutic trial only.

4. Positive and proven diagnoses must rest on the reproduction of the symptoms at will under specified conditions on three successive trials.

5. Treatment consists of avoidance and use of substitutes when necessary, but no restrictions must be imposed unless proven necessary. Injections of allergen and oral feedings are unsatisfactory.

6. Care must be taken to avoid undernutrition whenever diet restrictions are imposed.

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29. *Allergy to Drugs, Endocrine Products and Serum*

HORACE S. BALDWIN

DRUG allergy may be defined as the chain of characteristic signs and symptoms developing in certain individuals following the administration of doses of drugs which fail to produce symptoms in the vast majority of patients. The allergic type of response is to be distinguished from that due to the toxic action of the drug by the fact that the latter produces symptoms which are an exaggeration of its physiologic action.

So far as the mechanism of drug allergy is concerned, the accumulated evidence points to the same process as in true protein allergy. The earlier objections to this theory were based chiefly on the non-protein character of the drugs concerned and the failure to elicit positive skin tests. The newer knowledge of the importance of haptens in hypersensitivity supplies the missing link. Certain important experimental work is significant in this regard. Swift studied hypersensitivity to arsphenamine in guinea pigs. He was able to induce fatal anaphylactic response by sensitizing them with a mixture of guinea pig serum and arsphenamine, and then reinjecting the same mixture after the usual incubation periods. Shocking injections of arsphenamine alone, in this manner, yielded negative results. Apparently the mixtures of chemical substances and blood serum may cause combinations which alter the nature of the protein in such a way that when injected into animals of the same species from which it was obtained, it may react in the manner of a foreign protein. Similarly, on the basis of Obermayer and Pick's and of Landsteiner's observations that the specificity of proteins may be changed by azotizing them, Klopstock and Selter sensitized and then shocked guinea pigs with a combination of diazo-atoxyl and guinea pig serum, but not by the intravenous injection of diazo-atoxyl alone.

Drugs Causing Allergic Reactions

Drugs and chemicals which may cause allergic reactions may be classified as follows:

1. Alkaloids: Opium, quinine, belladonna, stramonium, hyoscyamus.
2. Essential oils and balsams: Cubebs, copaiba, sandalwood oil, turpentine.
3. Metals: Mercury, lead, nickel, arsenic, iron.
4. The halogens: Bromides and iodides.
5. Coal tar, benzol and methane derivatives such as antipyrine, iodoform, salicylic acid, creosote, salol.

6. Miscellaneous: Phenolphthalein, barbiturates, dinitrophenol, sulfonamides, penicillin.
7. Endocrine products: Liver extract, insulin, pituitary extract, estrogenic hormone.

The distinction between the symptoms of drug allergy and drug intolerance can be easily shown by charting certain drugs and listing the common symptoms associated with drug intolerance on the one hand, and drug allergy on the other. It will be seen that the symptoms of drug intolerance represent, for the most part, exaggeration of the physiologic and toxic reactions of the drug, whereas the allergic responses to most of the drugs have considerable similarity one to the other.

Aspirin.
Drug Intolerance: Disorders of hearing, dimness of vision, delirium, nausea, vomiting, diarrhea.
Drug Allergy: Angioneurotic edema, pruritus, urticarial and scarlatiniform eruptions, conjunctivitis with ocular edema. Coryza, asthma and death.

Quinine.
Drug Intolerance: Nausea and vomiting, tinnitus deafness, headache, disturbed vision, photophobia.
Drug Allergy: Truly eczematous eruptions with erythema, vesiculation, weeping and scaling, thrombocytopenic purpura, urticaria and edema.

Arsphenamines.
Drug Intolerance: Gastro-intestinal disturbance, colic, diarrhea. Hepatitis with jaundice. Encephalitis.
Drug Allergy: Dermatitis, exfoliative and erythematous eruptions, asthma, anaphylactoid symptoms. Herxheimer's reactions.

Opium, Codeine, Morphine.
Drug Intolerance: Contraction of pupils. Diarrhea and constipation, melancholia and dementia, headache, nausea and vomiting.
Drug Allergy: Erythematous eruption, pruritus. Asthma?

Barbituric-acid derivatives.
Drug Intolerance: Stupor, coma, mental confusion, nausea, excessive thirst, cyanosis.
Drug Allergy: Edema, urticaria. Fixed pigmentary eruptions.

Pituitary extract.
Drug Intolerance: Headache, gynecologic disturbances.
Drug Allergy: Urticaria, angioneurotic edema, respiratory difficulty, pruritus.

Insulin.
Drug Intolerance: Uneasiness, nervousness, weakness, faintness, sweating, thirst, incoordination, unconsciousness.
Drug Allergy: Urticaria, asthma, ocular edema, gastro-intestinal disturbance with cramps, and diarrhea.

Epinephrine.
Drug Intolerance: Tremor, nervousness, palpitation, precordial distress.
Drug Allergy: None.

Insulin Allergy

Insulin allergy may be very important in the handling of a patient with diabetes. An estimate of the incidence of sensitivity to insulin among the cases of diabetes at the New York Hospital would seem to indicate that the problem arises in about one out of a thousand cases. The most common form the sensitization takes is that of widespread urticaria and angioneurotic edema. In these patients the problem may occasionally be solved by shifting to a form of insulin obtained from some other animal source, but usually this is not effective. It may be necessary to desensitize by giving small, gradually increasing doses until the proper amount is reached. Usually, thereafter, there is no further trouble. One patient could take no insulin without reactions until crystalline insulin was given. With protamine insulin the same sensitivities may occur. Here, often, the greatest problem is the extent of the local reaction at the site of injection. As time goes on the amount of local swelling may diminish, but when this does not occur, it may be necessary to revert to the original type of insulin.

Allergy to Liver Extract

Allergy to liver extracts may be serious and take the form of acute constitutional reactions similar to those seen in serum allergy. Deaths have occurred following the parenteral administration of liver extracts to sensitive persons, and with the increasing use of liver extract as a tonic measure, in addition to its use in pernicious anemia, when the interval between doses is sufficiently long to allow sensitization to occur, it is a question whether it would not be wise to do skin tests with the extract prior to any injection. If sensitization is present, skin test reactivity is usually demonstrable by the intradermal method. The problem may be solved by the use of a highly purified extract of high potency starting with small doses and gradually increasing doses at frequent intervals. If this method is not successful it is necessary to rely on liver or its extracts by mouth. If the sensitivity is present for liver administered orally, it is possible to use the stomach extracts. Unfortunately at the present time these are not available for parenteral administration.

Estrogenic Hormones

Sensitivity to the *estrogenic hormones* does not seem to be a problem. It is possible, however, that individuals may be reactive to the peanut, corn or other oil that may be used as the medium or vehicle for the hormone substance, and if allergic reactions occur, this must be held in mind. A form of the hormone may be used in a vehicle to which the patient is not sensitive. Here again oral administration may be used with very little likelihood of allergic effect.

Toxoids

When the toxoids for tetanus and diphtheria were first being used a certain number of acute allergic reactions were reported. These seem to have been due to the type of peptone in the broth originally used for the toxoid. With the recent use of different peptones very few reactions occur. Certainly the widespread use of tetanus toxoid in the military services would indicate this. As a matter of fact, we shall probably have to wait for reports of its use in the armed forces before a definite answer can be given. At the present time it would seem to be true that allergy to the toxoids is of very little practical importance.

Serum Allergy

With the increase of the use of the toxoids for the prevention of tetanus and diphtheria, and with the tremendous strides in chemotherapy for the control of acute infections, it may be that before long the matter of serum anaphylaxis will be of academic rather than of practical importance. It is well, however, in this connection to remember that sensitivity to the chemicals may become increasingly important as their use increases and opportunity is given for sensitization to them to develop.

In certain cases, then, the use of therapeutic serums may be necessary. Before giving injections of foreign serum, certain procedures should be routine in every case. The patient should be questioned to discover a history of allergic disease or tendency, and the direct skin test with the serum should be carried out properly. An important point in testing is to use dilutions of the normal serum, from which the therapeutic antiserum is derived, rather than the antiserum itself. This latter may have had the original serum eliminated to a point below the threshold of the tests in the skin or conjunctivae. Outlined below are the diagnostic technics to be used routinely and without fail before any serum administration.

History. The patient must be questioned for:

Any allergy in the family including brothers and sisters, as well as antecedents.

Any past or present allergy in the patient, such as asthma, hay fever, urticaria and eczema, and any known food or drug allergy.

Any previous injections of serum with dates and results, such as serum disease.

Skin Test. An intradermal injection of 0.02 ml. of a 1:100 dilution of the animal serum about to be used. Read and record the result in ten minutes.

Eye Test. One to two drops of the animal serum 1:10 into the conjunctival sac. Read and record the result in ten minutes.

Having tested the patient for his sensitivity, the following outline should be used as a guide to the subsequent procedure.

Skin test negative and History negative	Serum administration safe by any route.
Skin test negative and History positive	Serum administration usually safe. Give slowly, have adrenalin ready.

Skin test positive and Eye test negative	Immediate reaction is possible, especially when given intravenously. Avoid intravenous injection until trial subcutaneous doses have been given safely. Then if intravenous therapy is necessary dilute the antiserum with saline and give slowly in spaced doses. Caution! Have epinephrine at hand, or give a preceding injection of it.
Skin test positive and Eye test positive	Immediate reaction is probable by any route, and may be severe and fatal. Avoid serum injection, or retest with a heterologous antiserum as directed above. The same rules apply to its use. Exceptions to this rule are rare.

So far as the management of serum sickness is concerned, no particular progress seems to have been made. One reason for this is the few cases of serum sickness now being seen, due to the use of the toxoids, chemotherapy, and the elimination of serum specificity from antitoxins at present being used.

Symptomatic measures such as the use of sedatives, analgesics, epinephrine, ephedrine and aminophylline are fairly effective. Histaminase has been found to be useless. Certain new drugs, such as benadryl and pyribenzamine, which are antagonistic to the pharmacologic effects of histamine, should have marked therapeutic value in relieving the most outstanding symptoms of the disease.

It is disappointing that, whereas the manifestations of drug allergy are increasingly important, any solution of the problem of handling them immunologically has made little progress. It represents a field in which investigation is greatly needed. Avoidance of reactions by substitution is the only present recourse.

30. Physical Allergy

JOSEPH HARKAVY

Introduction

Salter in 1860 reported a case of asthma induced by the application of cold to the instep. Behier in 1866 described his own urticaria following exposure to cold. Blachez in 1872 and Negel in 1884 reported similar cases. Wauchope, quoted by Bray,[1] recorded the case of Pepys, who suffered an attack of urticaria while walking in the park on a cold Sunday on February 8, 1663.

In 1923 Duke[2] reported a series of observations dealing with "reactions caused specifically by the action of physical agents such as light, heat, cold, mechanical irritation, freezing and burns, and in the case of heat sensitiveness, indirectly by the effect of mental or physical effort." These various symptoms were regarded by him as due to "physical allergy," the term indicating altered tissue reactivity in the broadest sense without the implication of an immunologic mechanism. The symptoms identified as resulting from primary contact with these agents are asthma, rhinitis, urticaria, angioneurotic edema, various other types of skin eruptions as well as generalized systemic reactions. These manifestations may follow immediately after exposure to the exciting factor or be delayed. They may be limited to the exposed surface, the so-called contact reaction, or affect distant structures away from the area of application, reflex-like reactions, in which case a more generalized response occurs.

In many instances, however, sensitiveness to physical agents has been noted to be secondary to underlying food or bacterial hypersensitiveness, the elimination of which was followed by disappearance of the physical allergy in question. Duke believes that the damage caused by physical agents may be the localizing factor of a skin reaction caused by food allergy. In support of this he cites patients who, after eating eggs, develop urticaria on exposure to cold, or after eating snails, may break out with an eczema where the skin had been sunburnt.

Pathogenesis

A number of theories have been elaborated which attempt to explain the underlying mechanism of physical allergy. These may be summarized as follows.

(1) **Autogenous Antigens.** According to Duke, the underlying mechanism may be due to the development of some new substance in the

tissues of the sensitive person, under the stimulus of light, heat or cold of certain intensities, similar to the new aggregations of protein molecules produced when proteins are subjected to these physical agents in vitro. The proteins thus altered may act as autogenous antigens to which the patient reacts in the form of asthma, rhinitis, etc. The investigations of Karady,[3] if confirmed, tend to support this point of view. Karady was able to shock guinea pigs with guinea pig serum exposed to -5° C. after previous sensitization with the same type serum whereas normal guinea pigs similarly injected showed no reaction.

(2) **Specific Physical Allergy.** In the opinion of some observers physical agents such as cold, light, thermal and mechanical irritation may act in a specific antigenic capacity and induce antibodies which are capable of being passively transferred by serum to the skin of non-sensitive individuals. Rajka[4] reports thirty-six cases collected from the literature in which passive transfer was achieved with serums of patients in whom reactions were induced by thermal and mechanical agents. To this number may be added cases reported by Duke and by Urbach due to mechanical stimuli and three cases by Epstein due to light sensitivity. These are regarded by Rajka as manifestations of true allergy.

(3) **H-Substance.** Lewis[5], Grant, Pearson and Comeau,[6] as a result of their studies of urticaria provoked by physical agents such as heat, cold or emotional stimuli in six subjects, came to the conclusion that such urticaria is dependent upon H-substance elaborated in the skin by the release of acetycholine, or substances very closely related to it in their pharmacologic effects, as a result of stimuli derived from the central nervous system and transmitted through the efferent peripheral nerves. They found support for this concept in the fact that blocking of a cutaneous nerve prevents, in its area of distribution, the development of the urticaria following the application of heat. These observations suggest that in addition to the immunologic processes there is also a nervous mechanism which may set up a series of changes releasing H-substance, not only in the skin but probably also in the mucous membrane of the respiratory tract. Locally this H-substance may be liberated through a system of nerves which Lewis designated as the nocifensor. The possibility that the nocifensor system of nerves by elaborating histamine-like substances may be responsible for non-allergic vasomotor rhinitis, and possibly for some types of so-called intrinsic bronchial asthma for which evidence of an underlying immune process is still lacking, is suggested by Alexander.[7]

(4) **Photosensitization.** It has been found that certain dyes and pigments such as eosin and chlorophyll may when introduced into living organisms cause them to become sensitive to the rays of the sun. Raab[8] showed that paramecia swimming in solutions containing a dye called acridine readily succumb on exposure to the sun whereas in the absence

of the dye they survive for long periods in the sunlight. Substances such as porphyrin may act as photosensitizers in man and their presence in abnormally high concentrations provides a condition in which photosensitivity may be expected. It has been assumed that the presence of such substances in the skin of patients is responsible for the symptoms. Sensitivity to light has been found, however, in the absence of porphyrin, hence other photosensitizing substances have been regarded as responsible for symptoms following exposure to light. These substances have thus far not been sufficiently identified and their mechanism is obscure.

Clinical Manifestations

The occurrence of physical allergy is not uncommon. It is seen in men and women with equal frequency. There may be a family as well as a personal history of allergy, which is especially evident in the contact type of reaction. Patients may therefore suffer from hay fever or asthma due to protein hypersensitiveness and in addition manifest reactions to physical agents. The latter include light, cold, ordinary heat as well as that induced by mental and physical effort, and mechanical irritation. The particular site involved is assumed to depend upon the location of the shock organ, whether inherited or acquired. Following exposure to any of these excitants, reactions may appear in the eyes, nose, bronchi, gastro-intestinal tract, skin, vascular as well as the hemopoietic system, suggested by the occurrence of eosinophilia.

Cold. *Contact reactions to cold* most commonly result in the prompt production of urticaria or angioneurotic edema. Exposure to cold may in susceptible individuals produce marked swelling of the face, eyelids, ears, excessive lacrimation and sneezing.

The temperature of cold-sensitive patients is usually normal, in contrast to that in the heat-sensitive patients in whom it may be subnormal. There are some persons who react to cold only after exposure to heat. Duke reports a man sixty-three years old who developed hives and angioneurotic edema especially at night after removing his clothes or after taking a cold bath. When rubbed with ice, nothing happened but when ice was applied to his chest after he was heated thoroughly by means of a nitrogen lamp and autocondensation current, generalized hives appeared which were promptly controlled by exercise.

Manifestations resulting from cold take the form of simple urticaria,[9] urticaria and purpura,[10, 11] urticaria and hemoglobinuria,[12] and anaphylactic shock followed by death as described by Horton.[13]

Pathogenesis. The mechanisms responsible for reactions to cold are similar to those which operate in other forms of hypersensitiveness to physical agents. In nineteen cases reported in the literature by various observers it was possible to demonstrate the existence of specific antibodies to cold on passive transfer. This leaves a large number of patients in whom no such antigen-antibody reaction has been shown to be present. There is reason to question the validity of these observations, and further study is necessary. The fact that some patients react to cold after being heated, others to cold water and not to cold air or vice versa, suggests that reflex vasomotor phenomena rather than specific mechanisms probably play an important part in the development of the presenting symptoms. Duke believes that the reflex type of response may be due to some derangement of the temperature regulating center. A more likely explanation for these reactions may lie in Lewis' concept of release of H-substance in the skin as a result of stimulation of vasomotor nerves by cold, heat or emotional stimuli. The disappearance of an existing cold or heat hypersensitiveness following the removal of a focus of infection, or avoidance of foods or inhalants to which a person may be sensitive, or the elimination of psychic disturbances as reported by Abramson in a patient with depression and urticaria due to cold, may be explained by the fact that the sensitizing agent, whether it be food or bacteria or the emotional factor, conditions the shock organ to respond not only to specific but also to non-specific excitants.

Treatment. Cold-sensitive patients should live in a warm climate. They should avoid exposure to cold, because once the condition is established it may be permanent. They should avoid cold drinks, cold baths and cold foods. Relief from cold can be obtained by heat of any kind including that generated by exercise. This also holds for asthma which may be relieved by exercise in the midst of an attack. It is important in this connection to distinguish between patients with true cold sensitiveness and those who are heat-sensitive, but who react to heat only after exposure to cold, inasmuch as the history may be the same, namely symptoms caused by cold. Heat-sensitive patients react only during the process of warming up and are made worse instead of better by heat. Tolerance to cold may also be established by exposing increasingly larger areas of skin to cold applications. Histamine desensitization, so-called, as advised by Roth and Horton, may be tried, in the form of subcutaneous injections of 0.1 mg. or less of histamine twice daily for two or three weeks. Results on the whole are unsatisfactory. Benadryl in 50 mg. doses, three or four times a day, has recently been reported on by McElin and Horton[14] as being beneficial in some of the cases of cold allergy.

Heat. Heat sensitiveness may result from direct contact or as a reflex type of reaction. The former is less common than the latter. The contact type of heat reaction is characterized by urticaria. It has been suggested that a special designation be assigned to the urticaria resulting from different causative factors, such as urticaria solaris, hiemalis, and dermographia ab igne. Local reactions develop at the site of contact and when the stimulus is severe enough, generalized reactions accompanied by an eosinophilia may follow. Local tolerance follows repeated application of heat, and general tolerance may result from a more extensive type of treatment.

The reflex type of reaction affects tissues away from the site directly exposed to the stimulus, and may be manifested according to Duke in several ways.

(1) It may occur as a result of heat irrespective of the source. This is found in markedly heat-sensitive patients in whom a temperature increase occurs as a result of mental or physical exertion and psychic stimuli. Crying or laughing is sufficient to cause a variety of reactions, such as generalized itching, burning redness of skin associated with an urticarial rash. These reactions may be controlled by application of ice-cold water or cold air on the skin.

(2) It may be caused by a local rise in temperature such as a nasal reaction caused by the application of a hot compress to the nose or the breathing of warm moist air. Either of these types of cases may react more markedly to heat if they are previously exposed to cold. In both instances therefore the reaction is due to a change of temperature from cold to heat.

(3) It may exist as a combined type of sensitiveness in which the reaction as a result of applying heat to one structure such as the nose or bronchial tubes may be greatly accelerated by the simultaneous effect of cold upon some distant structure. Duke records a case in which a nasal reaction caused by heat was accelerated by the effect of ice upon the skin of the body, and readily relieved by the local action of an ice compress on the nose. Patients in this category may also be subject to contact type of reactions from the same agents and also be pollen- or food-sensitive. Thus one patient may exemplify all three types of reactions.

The general symptoms resulting from heat sensitiveness are frequently observed in people after forty years of age and often follow an acute infectious disease such as pneumonia. They include in addition to generalized urticaria, extrasystoles, tachycardia, asthma, migraine and syncope. The reactions in heat-sensitive cases appear most markedly in the winter months and in changeable weather, especially when the nights are cold and when the body temperature of the patient is subnormal, 94 to 96° F. At such a time the patient may develop itching with or without whealing. Raising the body temperature may cause a disappearance of these symptoms. Some patients who may react in the early days of fall may be free from attacks at other times. Others, however, may experience their worst attacks during the hottest part of the day. Administration of adrenalin may be followed by relief of symptoms.

Pathogenesis. The mechanism involved, as in cold allergy, may be demonstrated in certain instances to depend upon an antigen-antibody reaction as in the cases reported by Lehner and Rajka[15] and Richter.[16] In the majority it is probably not of an allergic nature but mediated by the liberation of H-substance as described by Grant and his coworkers.[6]

Treatment. The basic principle in the treatment of these patients consists in gradual exposure to increasingly higher temperatures. Vaughan[17] describes a case in which the patient's hand was placed in water heated to 37° C. (99° F.). and kept there while the temperature was raised to 43° C. (110° F.). Tolerance by means of such a procedure may be followed by a full hot bath at 38° C. or 100° F. This form of treatment is carried out for four to six weeks. Favorable results in which the temperature is gradually augmented by means of diathermy have also been reported. Other workers use typhoid vaccine intravenously.

Light. Under ordinary circumstances exposure to sunlight is not only harmless to the normal individual but is beneficial, especially in disease states such as rickets and tuberculosis. In a patient hypersensitive to light, however, the usual contact may result in an urticarial or an inflammatory reaction. It is interesting to note that light urticaria is more common in women than men, and that sensitivity is increased in cases with menstrual disorders. The duration of hypersensitiveness may vary from a short time to many years. Practically all the reported cases reacted to the short wave visible blue rays and to ultraviolet rays.

Blum[18] classifies the diseases due to light sensitivity into two broad categories: skin lesions due to abnormal photosensitizing substances in the skin, urticaria solaris, and those produced by radiation which induces the sunburn of normal skin, that is, wave lengths shorter than 3300 Å ("polymorphic light eruptions").

Exposure to sunlight for brief periods in sensitive persons may be followed by the appearance of erythema confined to the exposed part (*urticaria solaris*). This is rapidly replaced by edema limited to the irradiated area and surrounded by a flare in the contiguous unexposed skin. The portions of the spectrum responsible for the urticarial lesion in the cases recorded by Blum were found to be in the region of 3900 to 5200 A. Duke's cases responded with urticaria to rays in the spectral region from about 3200 to 5000 Å and in the far red and infra-red. Rajka's case reacted to rays between 4000 and 5000 Å and occasionally to wave lengths of 4359 Å lying in the blue spectrum and abundantly emitted by the mercury arc. The latent period between contact and reaction may be a very few minutes in the majority of cases, although in some cases "several hours intervene."

Other manifestations following the direct exposure to the sunlight are various types of dermatitis, "*photodermatitis*," due to sensitization. These appear only after previous applications to the skin surface of photosensitizing substances derived from certain plants. They are variously designated as "fig dermatitis," "meadow grass dermatitis," an eruption occurring in persons taking sun baths who at the same time were in contact with certain meadow plants; "photodermatitis of vegetable origin," "berlock dermatitis," due to application of toilet water and subsequent exposure of the skin to sunlight or artificial ultraviolet radiation.

The *polymorphic light eruption* of the skin following exposure may consist of acute, subacute and chronic dermatitis, referred to by some dermatologists also as eczema-like polymorphic skin eruptions. The eruption is normally confined to the exposed portions of the face, especially the cheeks and forehead, and may also involve the neck, forearms and dorsal surfaces of the hands. According to Rasch[19] chronic polymorphic skin eruptions connote "a rash which causes intense itching, consists partly of oval and round, slightly raised erythematous spots of variable size, partly of irregular grouped vesicles and partly of small scab covered papules. On the hands which are diffusely swollen and cyanotic, there are found numerous infiltrated or urticarial erythematous plaques and remnants of pustules with a small central dimpled scab." Manifestations such as summer prurigo, eczema solare, prurigo aestivalis and summer acne are included in this category. Any one of these lesions may recur in the same form in one and the same individual or vary from one type to another following exposure to sun.

In addition to urticaria and eczematous types of reaction due to light the following group of cutaneous lesions have been tabulated by Hausmann and Haxthausen.[20] (1) Hydroa aestivale or vacciniforme—eruptions characterized by papulovesicular lesions resembling varicella which may leave permanent scars when the crust falls and be associated with congenital or chronic porphyrinuria or may occur in its absence; (2) pellagroid eruptions; (3) lupus erythematosus-like eruptions; (4) filiform verruca-like lesions described by Urbach and Wiethe;[21] and (5) xeroderma pigmentosum and melanosis of Riehl.[22] There are also intrinsic skin diseases which may be either precipitated or exacerbated by light, such as erythema exudativum multiforme, lupus erythematosus and rosacea. The exact role which light plays in these conditions is unknown.

Reflex-like reactions caused by light have also been described by Duke in two patients who manifested swelling of mucous membranes, sneezing and watery secretion upon exposing the face to the light of a thousand watt nitrogen lamp.

Pathogenesis. As already indicated, there are a number of factors which may be involved in the production of light reactions. These include (1) predisposing, (2) photodynamic and (3) allergic factors.

(1) Under *predisposing factors* may be considered the presence of an underlying infection or metabolic or endocrine disturbances which

"trigger" the individual so that exposure to light evokes a cutaneous response. Elimination of any one of these causes is frequently followed by the disappearance of the lesion. Stokes and Callaway[23] suggest that pathogenic bacteria especially of the hemolytic variety may by their metabolic activity, or by their destructive action upon the respiratory pigment brought to them by the blood stream, produce porphyrins which are absorbed by the organism and act as photosensitizing agents. Fungi of the Monilia genus in the intestinal tract of pellagrins have been suspected of producing photosensitizing substances.

In instances in which menstrual disturbances play a predisposing role in light sensitivity, correction by estrogenic hormones has been reported to be beneficial.

(2) In 1913, Meyer-Betz[24] observed that he became sensitive to the sun after injecting himself intravenously with 0.2 mg. of hematoporphyrin previously identified in the urine of two brothers who suffered from bullous eruptions diagnosed as hydroa aestivale. A short exposure caused edema and pigmentation, and the application of a Finsen ray to his skin resulted within fifteen minutes in deep infiltrations and hemorrhagic necrosis of the entire exposed cutis. This led to a more extensive study of porphyrins as substances either responsible for or associated with cutaneous and constitutional photodynamic effects. It has been found that porphyrins may be manufactured endogenously in the intestines by bacteria from hemoglobin, myoglobin and chlorophyll in vegetable foods, and are frequently present in diseases of the liver and various toxic states. They are excreted in the urine and stool as uroporphyrin and coproporphyrin. Different porphyrins vary in their photodynamic properties. While they may be present in the urine in diseases of the skin associated with light sensitivity, they may also be found in other conditions in which light hypersensitiveness comes into question, such as Landry's paralysis, and in chronic sulfonal, veronal or trional poisoning.

In addition to the endogenous porphyrins, numerous other exogenous substances have been discovered whose photodynamic properties predispose to light sensitivity. These include photosensitizing agents which may act as a result of topical application to the abraded epidermis, or when introduced parenterally through intravenous or oral routes. The majority of these photosensitizing substances have been classified by Stokes,[25] Blum,[18] and others as follows.

Essential oils: oil of citron, oil of lavender and oil-containing perfumes (eau de cologne).

Plants and plant substances: chlorophyll; buckwheat (responsible for fagopyrism in animals); St. John's wort; wilted "dubbeltje" plant; tribulus (the cause of geeldikkop in South African sheep, characterized by icterus and edema of the head); sudan grass and other grasses.

Dyes: eosin and eosin compounds, rose bengal, erythrosin, fluorescein, acriflavine, fabric dyes, acridine dyes and methylene blue.

Drugs: sulfonamides, barbiturates, gold, silver, arsphenamine.

External medicaments: coal tar, petroleum products, green soap, mercury bichloride, copper.

Bacteria and certain viruses (smallpox, chickenpox, herpes simplex).

The action of exogenous photodynamic agents is not altogether clear. According to Blum the sensitizing mechanism is closely associated with the oxidation mechanism of the cell. Other theories in regard to photodynamic action are more extensively discussed in Blum's comprehensive monograph.[18]

(3) Evidence in support of an allergic mechanism in hypersensitiveness to light has been brought forth by various students. Duke was one of the first to present such proof. Callaway,[26] Flarer,[27] Stein,[28] Bernstein,[29] Jansion and Pages,[30] and Rajka and Epstein[31] were likewise able to demonstrate the presence of sensitizing antibodies in the serums of light-sensitive patients by passive transfer. Epstein was able to show that the serum of two out of six patients with prurigo aestivalis contained antibodies which, when transferred, elicited in one instance an urticarial reaction, and in another a prurigo-like lesion, eight and nine days respectively following injection and irradiation. On the basis of these and other observations he concludes that while the theory of primary photosensitivity, which he refers to as phototoxicity, is concerned chiefly with the mechanism of photodynamic action, and with so-called sunburn effect, it fails to explain in his cases (*a*) delayed reactions in light tests, (*b*) reactions at sites remote from the irradiated part, (*c*) the provocation of prurigo lesions by radiation other than light, namely alpha and gamma rays, (*d*) passive transfer with delayed reactions. He considers these phenomena as supporting the concept of allergy, photo-allergy, rather than primary photosensitivity or phototoxicity, although he recognizes that other factors besides sensitivity to light and allergy may contribute to the pathogenesis of prurigo aestivalis.

Sensitivity to roentgen radiation has been reported by Paltrinieri,[32] Richet,[33] and Miescher.[34] Miescher expresses the opinion that actino proteins may be formed under the stimulus of roentgen rays which lead to the production of specific antibodies. These newly formed substances may be responsible for the wave-like exacerbations of erythema subsequent to roentgen ray exposure of the skin, similar to the recurrent exanthemata seen in serum sickness. There is, however, no evidence of the development of any such antigenic components. The subject is further confused because of the fact that the cumulative effects of the roentgen rays which may account for these phenomena have to be taken into consideration. The observations of Marks,[35] who found that sulfanilamide sensitizes the skin to roentgen rays and that such sensitization persists long after the drug has been discontinued, suggest that the latter has photodynamic properties.

Treatment. According to Stokes and Beerman[36] the treatment of patients with light dermatoses is divided into the general and local. The *general* aspect of this problem concerns itself with the diagnosis and proper evaluation of the different underlying factors involved in any one case. Inasmuch as some patients can tolerate winter but not summer sunlight, others sunlight in a moist but not in a dry climate, removal to a locality best suited to each individual is of paramount importance. Foci of infection, when present, should be eliminated. Metabolic disturbances must be properly corrected. Endocrine disorders should be treated with indicated hormones. Progressive light desensitization by daily exposure to ultraviolet lamp, successfully accomplished by Hurst[37] in one of his cases, may be attempted. If that is impossible complete avoidance of sunlight by staying indoors may be necessary in highly sensitive cases. The eyes should be protected by colored glasses since even short exposure may cause temporary blindness.

Local treatment consists in protecting the skin by proper clothing, veils and dark gloves, and avoidance of photosensitizing substances such as perfumes, etc. Numerous local preparations have been described for the purpose of filtering out the offensive rays. Bachem and Fantus[38] have evolved a number of finished "cuticolor" preparations for that purpose. The basis of these is the "cuticolor" titanium dioxide, the formula of which is: red ferric oxide 6.0 mg., yellow ferric oxide 8.0 mg., titanium oxide 86.0 mg., mix by trituration. This may be put up as a lotion, paste, ointment or cream salve.

Mechanical Irritation. Under ordinary circumstances the application of pressure or stroking of the skin is not associated with any discomfort or visible alteration of the part affected. In sensitive individuals dermographia or erythema, which has been called factitious urticaria, may follow stroking or scratching of the skin. It seems to be similar in many respects to that caused by light or cold. Duke describes a case of a boy subject to asthma in whom the slightest scratching was followed by hives, itching, and marked urticaria, limited, however, to the irritated area. This reaction exhausted the spot so that further irritation was without any apparent effect. In other words, a certain amount of tolerance was achieved by scratching. The same sequence of events occurred, but to a lesser degree, when larger areas of skin were frequently scratched. The result of the repeated mechanical stroking was to relieve the patient completely of the sensation of itching and reduce the amount of erythema. Edema, however, appeared invariably following scratchings. The degree of relief was on the whole short-lived. Mechanical irritation of large areas resulted in generalized itching and eosinophilia. Adrenalin was without effect.

Urticaria due to pressure must be distinguished from urticaria factitia. Whereas the latter is induced by superficial scratching, as stroking of the skin, the former develops after a latent period varying between two and twenty-four hours, and is limited to the area receiving severe pressure. It appears either as an urticaria or as an edematous swelling of the feet after walking, of the hands when the person is at work, and of the buttocks when he is seated.

Pathogenesis. The pathogenesis in pressure urticaria may, in some respects, be similar to that observed in light urticaria. Predisposing factors, such as infections, various intoxications and porphyrinuria, as described by Andrews,[39] and Gottron,[40] may play a role in the development of these manifestations. The mechanism involved in the development of factitious urticaria in the cases studied by Walzer,[41] Liebner,[42] Urbach and Steiner[43] is regarded as probably that of physical allergy. The evidence for this is based on the demonstration of specific antibodies in the serums of patients sensitive to mechanical stimuli on passive transfer. In the majority of cases, however, traumatic liberation of H-substances in the skin is considered as most frequently responsible for the whealing.

Discussion

Cold, light, heat and mechanical irritation may induce cutaneous, respiratory and systemic symptoms expressed as urticaria and other dermatoses, vasomotor rhinitis, asthma, gastro-intestinal symptoms, and shock-like reactions similar to those occurring as a result of sensitization to foreign protein. The exciting agents may affect the various existing shock tissues by virtue of direct contact or at points distant from the point of application of the irritant. Duke refers to the latter as reflex-like reactions. The contact type of reaction is considered by him to be due to direct stimulation of the peripheral efferent nerves. In the reflex-like cases the stimulus is exerted upon the sensory or afferent nerve terminals, which transmit impulses to the autonomic nerve centers which may be hyperreactive in sensitized persons. This lability may be the result of some injury, such as a previous infection, since many patients who are subject to reflex-like reactions caused by sensitiveness to temperature change date the onset of their symptoms to a serious illness such as infectious disease. Impulses arriving from the disturbed heat regulatory center may be transmitted via the autonomic nerves and give rise to an explosive reaction which, in the allergic person, may be followed by characteristic manifestations such as asthma, coryza and urticaria. This theoretical explanation may be correlated with the concept of Lewis, Grant, et al., who attribute the development of urticaria, resulting from physical or emotional stimulation, to impulses arising in the central nervous system and transmitted through the cholinergic nerve fibers with the liberation of H-substance in the skin. This is comparable to the release of H-substance which is supposed to take place during the immunologic reactions associated with allergic phenomena.

The successful demonstration of passive transfer (the Prausnitz-Küstner reaction), with serums obtained from a number of patients sensitive to physical agents such as cold, heat, sun and mechanical irritation, similar to that observed in instances of sensitization to foreign proteins, has caused a number of investigators to identify the reactions resulting from these physical stimuli with allergy. However, this work will bear repetition. Inasmuch as it is difficult to assume that physical agents combine directly with the protein-like reagin in the same way as other allergens to liberate H-substance, regarded as the non-specific activator of the allergic response, Rajka proposes a modification in the currently accepted theory of the allergic reaction in order to correlate the operations of various types of allergy within the framework of a common mechanism. To this end he endows the reagin with the properties of a catalyzing agent which, when activated by specific chemical (proteins) or physical stimuli, accelerates the formation of H-substance from the normal metabolic constituents of the cell. This theory, which is highly speculative, adds but little to our understanding of the fundamentals involved in reactions to physical excitants.

To further implement the concept of physical allergy, Rajka points out that, just as in protein hypersensitiveness, positive skin tests are induced in sensitive persons by specific physical irritants in intensities ineffective in normal persons. Whereas light, cold and heat elicit urticaria in the person responsive to physical agents, this is not the case in the normal person. Moreover, improvement or cure can be achieved in a number of patients by the repeated application of the homologous physical irritant.

In addition to the aforesaid mechanism, in cases of light sensitivity, the role of endogenous and exogenous photodynamic substances must be taken into consideration. These substances may cause the development of erythematous or eczematous types of reactions not only in allergic persons but probably also in so-called normals.

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Section IX

TECHNICS

31. *Skin Testing*

MATTHEW WALZER

Introduction

THE skin test has been the most important single influence in the development of the subject of allergy. It was first employed in a crude form by Blackley in 1873, and again by Dunbar in 1903, in experimental studies in hay fever. However, the skin test did not come into its own as a diagnostic procedure until von Pirquet's scratch test with tuberculin (1907) and Schick's intracutaneous test with diphtheria toxin (1910) attracted attention to the possibilities of detecting immunologic states in this manner. Then followed the fundamental studies of Schloss (1912) and Walker (1916) which served to establish the practicability of using the scratch technic as a diagnostic procedure in human forms of hypersensitiveness. Cooke (1915) developed the intracutaneous technic for the same purpose. Starting with these two basic technics for detecting the presence of hypersensitiveness, the study of allergic diseases progressed rapidly.

In the early years, attention was concentrated on the improvement of the testing technics and of the materials employed for this purpose. This led to an overemphasis on the importance of this diagnostic procedure, so that, for a long time, progress in the field of allergy depended almost entirely upon development of the skin test. The failure to obtain positive cutaneous reactions in all forms of allergy was attributed to an inadequacy of testing materials and technics, and it was generally anticipated that the etiologic factors in all clinical forms of hypersensitiveness would eventually be revealed by improvements in testing methods. After more than a quarter of a century it has become apparent that these earlier hopes and prognostications for the future of skin testing were too optimistic.

Today, while the importance of the skin test is fully appreciated, its limitations as a diagnostic procedure are also realized. The clinician has learned that the skin test is, at best, only a relatively crude diagnostic technic which, though relatively simple in its performance, is subject to many pitfalls. Considerable experience is needed for its proper application and for the effective interpretation of the reactions obtained with it. It is now common knowledge that the skin test is of diagnostic aid only in certain forms of allergic illnesses. In others, even when skillfully performed, it is either of limited value or completely useless.

A positive skin test is only the first phase in this diagnostic procedure; more difficult but more important is the interpretation of such reactions. Analysis of the mechanism involved in the formation of cutaneous reactions has revealed many factors which render their evaluation a far from simple procedure, for non-specific as well as immunologic factors share in the production of reactions. Furthermore, cutaneous reactions may result from different immunologic mechanisms in the same patient and may, therefore, vary in clinical significance. Even more disconcerting to the clinician is the realization that even when all the reactions are produced by the *same* immunologic mechanism, as for example the atopic reagin, they are, nevertheless, not of equal importance. Under such circumstances, it becomes obvious that at least a working knowledge of the principles involved in skin reactions and considerable experience are necessary prerequisites for the effective employment of the skin test as a diagnostic procedure.

In the atopic group of allergic illnesses, i. e., those in which an hereditary predisposition is the primary etiologic factor, the specific skin reactions obtained by testing with allergens are almost always mediated by the antibody known as the atopic reagin (or the skin-sensitizing antibody) which is present in the blood and tissues. In fact, skin testing in atopic illnesses can be looked upon as a method of detecting, in the atopic patient, the presence of atopic reagins for allergens or excitants which, in the opinion of the clinician, may be the cause of the patient's symptoms. In those *atopic* illnesses which are not mediated by reagins, the skin test cannot be relied upon to reveal diagnostic information concerning offending allergens.

Unfortunately, even the detection of reagins in a patient does not conclude the diagnostic investigation, for one finds these antibodies in non-atopic as well as in atopic persons. Moreover, even in the atopic patient, reagins may fail to produce clinical expressions of hypersensitiveness although the patient is adequately exposed to the offending allergen. Unless, coincidently, there is present in the patient a "shock tissue" which is susceptible to the excitation produced by a reagin-allergen reaction within its cells, no clinical symptoms of allergy result. In establishing the presence or absence of reagins by skin testing, the clinician is, therefore, able to obtain information concerning only one of the several factors which combine to produce the allergic reaction.

Diagnostic Value

The specific diagnostic value of the reaginic skin reaction is further limited by the fact that the presence of the atopic reagin is not pathognomic of the existence of atopic hypersensitiveness in a person tested. It has been repeatedly demonstrated that, with the proper excitant, reagin production may be effected in non-atopic as well as in atopic persons. Ascaris lumbricoides is an ideal antigen for this purpose not only in human beings, but also in some animals. Horse serum, insulin and liver extract also commonly excite reagin formation in non-atopic as well as in atopic persons. As a rule, however, reagin production in atopic persons tends to be stronger and more lasting than in non-atopic. Moreover, while atopic patients are inclined to produce reagins for common foods and inhalant allergens, many of which have relatively weak antigenic properties, the non-atopic person usually lacks this tendency. His reagin-producing capacity is restricted to a few allergens such as parasites and animal serums, which undoubtedly possess antigenic properties of an unusual nature.

All of these circumstances combine to make the diagnosis of atopic hypersensitiveness by skin testing a rather complicated procedure which, in the hands of the neophyte, has often been misleading and of questionable value. However, the fact that skin testing has not turned out to be a simple and completely reliable technic does not detract from the fact that when it is intelligently and skillfully performed, it remains the most effective diagnostic procedure in reaginic allergic disorders. Therefore, it becomes the duty of the clinician, who expects to rely on the skin test as an aid in diagnosis, to study the technic thoroughly in order to understand its possibilities and limitations. Only in this way can he hope to derive the greatest benefits from its application.

The most outstanding characteristic of the atopic reagin is its pronounced affinity for the skin and mucous membrane. Passive local sensitization of the ophthalmic, respiratory and alimentary mucous membranes may be accomplished with the same regularity and success which is attainable in passive sensitization of the skin. Hence, there is sound rationale for testing the skin in atopic sensitivities, even when that tissue does not appear to be participating in the allergic reaction and the symptoms seem to involve only the mucous membranes.

Skin testing yields the most satisfactory results in allergic disorders of the *respiratory tract.* The direct contact between the inhalant allergen in its natural state and the exposed sensitive mucous membrane is, in a sense, reproduced by the cutaneous test in which there is direct contact of the skin with an extract of fresh allergen in the natural state. Hence, in allergic rhinitis, especially in hay fever, and in asthma, conditions in which inhalants play an important role, the skin test yields highly gratifying results.

In disturbances resulting from allergy to *foods or medicaments*, the diagnostic effectiveness of skin testing is considerably reduced for a variety of reasons which will be discussed later.

In cases of *atopic* (intrinsic) *dermatitis* and *neurodermatitis*, and, to a less extent, in migraine and gastro-intestinal allergy, conditions in which foods are apt to play an important etiologic role, the skin test has, nevertheless, contributed significant information with sufficient frequency to make it a worthwhile diagnostic procedure.

In *chronic urticaria*, *angioneurotic edema*, *papular urticaria*, *vernal catarrh*, and *drug sensitivities*, skin testing has been of practically no assistance. This inadequacy is based not upon limitations of the technic or of the materials employed, but upon the fact that reagins play little or no demonstrable part in the mechanism of these conditions. When reactions are obtained—and they frequently occur in papular urticaria and vernal catarrh—they are usually referable to associated atopic disorders and have no direct demonstrable bearing on the symptoms under investigation.

Technic

In testing the skin for atopic hypersensitiveness, one of two technics is generally employed. Both methods, the "scratch" and the "intracutaneous," are based upon the same immunologic principles and seek to accomplish the same purpose. Each method presents certain advantages and limitations. Some workers learn to use both methods, employing for each case that technic which best suits the circumstances. Others seek to derive all of the advantages of the two procedures by using them, in succession, on the same patient. Most clinicians concentrate on one technic and perfect it to the point where, in their hands, it provides more information than is obtained by others with the less skillful application of both methods.

The skin test is now so widely used that a detailed description of this procedure would be superfluous. Hence, only a brief discussion of the basic features of the two types of testing will be presented. There are, naturally, many variations of these technics, since clinicians differ in their preferences for the types of materials to be used and for the methods of their application. The following discussion will deal only with the more typical forms of the scratch and intracutaneous methods of skin testing.

Scratch Test. In the "scratch" or "dermal" technic, the allergenic material to be tested is gently rubbed into a superficial scratch in the skin. The tests are usually performed on the flexor surface of the forearm in adults and on the back in infants and young children. Previous to testing, the skin is cleansed with 70 per cent alcohol and allowed to dry. With the skin under tension, a superficial abrasion of from 2/16 to 3/16 inch is made by the use of a sterile needle or a semi-sharp cutting edge. This is done without drawing blood. A drop of saline or glycerin extract of the allergen is then applied and gently rubbed into the scratch. The material is not allowed to dry and, in the case of saline extracts, may need to be replenished from time to time. When a powdered allergenic extract is employed, the scratch is moistened with one or two drops of a one-tenth-normal solution of sodium or potassium hydroxide. The amount of the powdered allergen which can be transferred on the terminal 1/8 inch of a flat toothpick is then placed in the alkaline drop and gently rubbed into the scratch with a few strokes of the toothpick. The alkaline solution is replenished whenever necessary. A control test is made with the same technic, except that diluent alone is rubbed into the scratch.

From fifteen to thirty minutes later, when the reaction has reached its height and while the borders of the reactions are still sharply defined, the test material is gently wiped off and the results of the test and control are compared and recorded.

When hypersensitiveness to the allergen is intense, the skin reaction tends to develop very rapidly. Under such circumstances, there is a possibility that enough allergen may be absorbed from the site of the test into the circulation to produce a constitutional or systemic allergic reaction. Since excessive cutaneous reactions are of no greater diagnostic value than less pronounced ones and may induce systemic or constitutional symptoms which are extremely dangerous to the patient, every effort should be made to avoid producing them. As soon as a skin reaction shows signs of becoming unusually pronounced, the test material should be washed off.

When multiple tests are performed at one sitting, the scratches are made an inch or more apart and in widely spaced parallel vertical rows. Care is exercised to prevent contamination of the allergenic material on one test with that from another. This may result from the running together of liquid extracts on neighboring sites or from the improper cleansing of implements used in the performance of multiple tests.

The number of tests performed at one sitting is governed by many considerations, the most important being the age of the patient, the intensity of his symptoms, the history of his known sensitivities and the potency of the allergens employed for testing. In the average adult, from twelve to twenty tests may be made at one time. When negative or only occasional weak reactions are being obtained, this number may be increased.

Intracutaneous Test. The "intracutaneous" or "endermal" test involves the introduction of an allergenic extract into the superficial layers of the skin. Since an injection is made, sterile extracts and syringes must be used. The outer aspect of the arm is the site most favored for this test although some workers employ the forearm, thigh, or back. The skin should be cleansed with 70 per cent alcohol. Allergenic extracts in dilutions shown by experience to be relatively safe are used for the test. For injection a one milliliter syringe, with a 26 to 27 gauge needle, 3/8 inch in length, is employed. It is desirable that the plunger fit tightly in the barrel and offer a slight resistance to pressure of the operator's finger. An injection of 0.01 ml. of the test extract into the most superficial layers of the skin is made. This will produce a wheal about the size of a large pinhead. As a control, a similar injection of sterile extracting fluid is made in a neighboring site. If more than one test is performed, injections may be made in well spaced rows on the arm, each test being at least 1½ inch from its neighbor. Since it has been shown that a strong reaction on the arm tends to increase the size of neighboring reactions, especially those directly above or below it, it is preferable, in the performance of multiple tests, to arrange them in *horizontal* rows around the arm, avoiding the medial aspect. The rows should be parallel and, if possible, 3 or more inches apart.

A technic for intracutaneous testing which has proved satisfactory, in my experience, will be briefly described. The syringe is loaded with about 0.2 ml. of test extract and then held in the upright position and any air which may be present in the syringe is expelled. This precaution is necessary to prevent the injection into the skin of an air bubble which may cause the allergen to splash as it is introduced into the tissues, producing a false positive reaction. The skin, which has been wiped gently with alcohol, is put under tension by grasping the soft part of the arm posteriorly. Starting with the syringe at an angle of about 45 degrees to the arm, with the bevel *down* and facing the skin, the needle point is gently inserted with a forward lifting motion as if to pick up the skin with the very tip of the needle. As the tip engages and enters the skin, the "pick up" motion is gradually converted to a forward pressure while the barrel is lowered to eliminate the angle it previously formed with the skin's surface. As a result of the insertive pressure most of the bevel, by this time, has penetrated the skin. That part which is still outside should then be in complete contact with and closed by the skin surface. At this moment, the index finger, which has been resting on the plunger, forces the desired amount of extract into the skin. Even when the bevel is in poor apposition with the skin and some of the fluid escapes externally, enough usually passes through the needle point to raise the necessary test wheal. When properly performed, the technic is simple and practically painless. It presents no greater discomfort to the patient than is afforded by the scratch technic.

The number of tests made at one sitting will be governed by the same factors enumerated in the discussion of the scratch technic. Because the allergen is actually introduced into the skin and cannot be removed when reactions become too marked, caution and experience become essential prerequisites for the safe performance of intracutaneous testing. Otherwise, serious constitutional reactions, even fatalities, may result from the use of this technic. For these reasons, the number of skin tests performed at one sitting is generally less than the number performed when the scratch technic is employed. In the average adult with no history of acute sensitivity, not more than from twelve to eighteen tests are advisable at one sitting, in groups not to exceed six, and at intervals of about one-quarter hour. In infants and children, the number will naturally be much less, and when strong sensitivity is suspected, single tests in high dilutions should be made. These factors will be discussed again under constitutional reactions.

With the intracutaneous technic the skin reaction tends to develop more rapidly than with the scratch. Therefore, the reading time, about eight to fifteen minutes, tends to be shorter than in the scratch technic. The reactions are read at their height, when the borders of the wheals are sharply defined.

Descriptions of Reactions. The fully developed *positive cutaneous reaction*, resulting from skin tests with the intracutaneous and scratch technics, usually consists of a wheal, irregular in outline, surrounded by an erythema and accompanied by a variable degree of pruritus. The intracutaneous technic tends to produce stronger reactions than the scratch unless the materials employed in the latter method are highly concentrated. In the strongest reactions a wheal may grow to be several centimeters in diameter but, as previously stated, reactions of this size are dangerous and undesirable. The more pronounced the wheal, the greater is its tendency to be irregular in outline and to exhibit pseudopod formation. In a weak reaction the wheal tends to be small and in the scratch technic may even be absent entirely, in which case the erythema may present the only evidence of a positive reaction.

The erythema or areola which surrounds the wheal varies in outline, diameter and intensity with each reaction and with the response of the individual skin to trauma. One occasionally finds skins which exhibit wheal formation with little or no surrounding erythema, even in marked positive reactions.

Pruritus is another characteristic which varies with the individual and with each reaction. It may be proportionately greater than the other components of a reaction or, in some skins, may be absent entirely, regardless of the size which the reaction attains. Of the three components of a positive test pruritus is of the least clinical significance.

A test is considered to be positive when it exceeds the control in the size of the wheal or erythema or both. The larger the control the less trustworthy are the results of the tests.

Grades of Reaction. *Reactions are graded* according to arbitrary standards which each worker adopts for his own purposes. They may be read according to commonly used scales, such as O, +, ++, +++, ++++, or as negative, slight, moderate, marked, and marked-plus. Experienced workers try to avoid reading reactions mechanically and adopt reading methods to fit their particular needs. Some clinicians record, separately, the degree of wheal, erythema and pruritus. Most workers tend to average all three components into one reading, placing most emphasis on the size of the wheal. In view of the absence of uniformity in reading and recording reactions, it is essential for each investigator to describe, in his publications, the standards which he employed in these procedures.

A scale for reading reactions, which is based on actual measurement of the size of the wheal and erythema, loses in value in instances in which the control reactions are not completely negative. Because the non-specific response of the skin to injury varies so widely at different ages and in different individuals of the same age, more useful clinical information is often gained by reading reactions on the basis of comparative size in the same individual than by reading them according to a fixed scale of measurement for all cases. Nevertheless, the latter technic has a definite field of application in research and in experimental studies.

Technical Errors. There are common technical errors in the performance of skin tests which should be minimized or avoided, if possible. For example, the element of trauma in skin testing should be reduced to a minimum for, as Lewis has proved experimentally, whealing is part of the cutaneous response of the skin to injury. Some skins respond excessively to the slightest injury. In such cases it becomes difficult to determine whether the reactions are traumatic or immunologic in nature.

With the scratch technic the best results are to be obtained with a short scratch, made so superficially as *not* to draw blood. There is little need for vigorous protracted rubbing of the allergen into the scratch. A few light strokes of the applicator are usually sufficient.

Another common error in skin testing is the crowding of many tests into a small area. They should be well spaced, in view of the fact that strong reactions tend to influence neighboring tests. The stronger the reactions and the greater the number of positives obtained at one time, the greater the likelihood of obtaining pseudo-positive tests. Only when reactions are few and weak or absent entirely should more than the usual number of tests be performed at one sitting.

The common practice of injecting as much as 0.05 to 0.1 ml. in the performance of an intracutaneous test should be condemned. The initial trauma resulting from the injection of such a large amount of fluid into the skin is sufficient to produce non-specific whealing. This is not only misleading in itself but impairs the diagnostic value of many tests which produce only slightly positive reactions but which, nevertheless, are specific and of diagnostic significance. Some workers attempt to circumvent this difficulty by lengthening the reading time in this technic on the assumption that specific positive reactions are absorbed more slowly than the non-specific ones. This premise merely adds an additional unknown factor to a technic which is already handicapped by too many variables.

In performing the intracutaneous test, every effort should be made to reduce injury to the skin to a minimum. To accomplish this, sharp needles of narrow gauge should be used. The injection should be made as superficially as possible. Rotating the needle either during or after its introduction into the skin adds nothing to the effectiveness of the technic but definitely increases cutaneous injury. This is particularly true when the needle point has not been properly sharpened and is imperceptibly bent or lacks a tip. Furthermore, sound technic in the performance of a test does not require that the entire bevel be buried in the skin. It is not only possible but preferable that only part of the needle point be inserted into the skin. In this way, tissue injury is diminished and the unpleasant sensation associated with insertion of the needle may either be eliminated or reduced to insignificant proportions.

Comparison of the Scratch and Intracutaneous Technics. Such a comparison reveals that certain advantages and limitations are associated with each procedure. There is no doubt that the scratch technic is the less expensive and less complicated of the two methods. It dispenses with many requirements needed for intracutaneous testing, such as a large supply of syringes with carefully sharpened needles, an ice box for the storage of extracts, and the necessity for sterile precautions in the preparation as well as in the use of extracts. The scratch technic diminishes the likelihood of constitutional reactions which the careless application of the intracutaneous test tends to produce. For this reason, the scratch technic is by far the safer method for the novice who is not fully cognizant of the dangers of testing and of the steps for preventing and counteracting untoward reactions which may result from the procedure.

On the other hand, the intracutaneous technic is superior to the scratch method in many important respects. It is generally conceded to be a more sensitive and, therefore, a more effective diagnostic procedure than the scratch. However, the intracutaneous technic, when crudely performed or when inferior materials are used, may produce many false or non-specific reactions. This objection, which, in the earlier days of testing, was directed almost exclusively at the intracutaneous technic, now frequently applies to the scratch method as well. This has resulted from the increased concentration of the allergens used in scratch testing in the attempt to increase the effectiveness of this technic. This end has been achieved with many allergen extracts but has naturally brought with it a reduction in the specificity of the reactions obtained, since concentration of extracts tends to increase their irritating properties in the skin.

Probably the greatest advantage of the intracutaneous method is its adaptability and flexibility. Testing materials may be varied in concentration to suit the needs of the occasion. The same materials used in skin testing may be used for ophthalmic and nasal tests and for treatment. Its greater flexibility and sensitiveness make the intracutaneous test the technic of choice in research procedures. It is particularly significant that the Prausnitz-Küstner reaction and its various modifications, which form the basis for some of the most fundamental immunologic investigations in the field of allergy, may be properly elicited only with the intracutaneous technic.

Many clinicians combine the use of the scratch and intracutaneous technics in their diagnostic investigations. They minimize the likelihood of constitutional reactions by performing their preliminary tests with the scratch technic. Those allergens giving negative reactions are then retested by the more effective intracutaneous method with little danger of inducing untoward reactions.

There is some justification for this combined use of both technics by those who are entering the field of allergy and are seeking to avoid constitutional reactions. There should be little need, however, for the experienced physician to burden himself with this duplication of diagnostic procedures. A thorough knowledge of the intracutaneous technic should eliminate the necessity for preliminary investigation by the scratch method. Constitutional reactions from skin testing are now uncommon in the experience of those workers who have taken the necessary measures to prevent them, such as attention to the patient's allergy history and the use of standardized extracts.

Modifications of Scratch and Intracutaneous Tests. Many modifications of the two types of direct testing are being employed. Some workers advocate repeated skin puncture with a sharp needle through a drop of allergen placed on the skin. Others, as a substitute for a skin scratch, rotate the end of a fine narrow borer or screw driver, about 1/32 inch wide, at a site on the skin and rub the allergen into this slightly abraded area. In another type of procedure, which is now being developed, the allergen is mixed with a substance of high cutaneous penetrative power and is gently rubbed into the skin. In another novel technic the allergen is introduced into the skin by electrophoresis. These and other variations of the basic skin testing technics are adapted to fit the particular needs and preferences of the investigator. However, in all of these procedures, the same broad immunologic principles apply which obtain in the original scratch and intracutaneous technics. Time and experience will eventually determine whether any of the suggested modifications present advantages of sufficient importance to justify their substitution for the standard procedures which have hitherto been employed.

Allergen Group Testing

In an effort to simplify testing, allergens of a single or of related biologic groups are frequently pooled and tested by a single "group" test. This practice may be employed as a possible time-saving diagnostic procedure for excluding sensitivity to various unimportant groups of allergens.

It is not trustworthy for many reasons. The presence of one irritating extract in the mixture may cause a non-specific positive reaction which implicates the entire group. On the other hand, a weak sensitivity may be missed as a result of a too great dilution of each allergen in the mixture. In patients sensitive to many types of allergens, all "group" extracts tend to be positive and therefore supply little specific information. Moreover, in using mixtures of allergens which are extremely potent, as in the case of fish, animal danders and nuts, the likelihood of inducing constitutional reactions in patients sensitive to these antigens is increased. And finally, a positive reaction to a "group" test necessitates subsequent retesting with all of the allergens which constitute that group. This requires a duplication of effort which reduces or may even eliminate any time saving value which the procedure may possess. All in all, "group" testing is a crude practice of questionable merit which should not be applied in testing with important types of allergens.

Instead of attempting to test all cases routinely with hundreds of allergens by means of a large series of "group "tests—a common practice among inexperienced and misguided clinicians who, in most instances, are receiving their clinical direction from pharmaceutical firms—one may obtain more specific and trustworthy information by tests with a few well chosen representatives of each biologic group of allergens. Because patients tend to be sensitive to *types* of allergens which vary with each case, and because the number of the patient's sensitivities in any biologic group is more apt to be multiple than single, testing may often be simplified by skillful selection of allergens which are most representative of the groups.

Constitutional Reactions

The dangers associated with constitutional reactions have played an important role in the evolution of the technic of skin testing. Because such reactions are likely to occur sooner or later in the experience of all who practice allergy, either as a result of skin testing or following an injection during the course of specific hyposensitization, a thorough knowledge of their symptomatology, etiology, treatment and prevention is essential.

Cause. Constitutional or systemic reactions result from the absorption of allergen from the site of test or injection into the general circulation in amounts exceeding the tolerance of the patient. They may be "immediate," i. e., within a few minutes following contact with the allergen, or they may be "delayed" for many minutes or for hours. The rapidity of their onset and their severity depend on several factors, the most important of which include the degree of sensitivity of the patient, the amount and concentration of the allergen employed and the method of its application. The earlier the onset of the reaction following the test (or injection), the more severe and dangerous it is likely to be. Delayed systemic reactions can usually be controlled easily with an injection of epinephrine and do not present the acute, alarming picture which characterizes the severe immediate type of reaction.

Constitutional reactions may occur with any method of skin testing, but they are much more common with the intracutaneous technic since this procedure involves the actual introduction of the allergen into the body. They may, however, occur following the scratch test, especially since it has become a common practice to use highly concentrated allergens. The fact that the allergen is applied to the surface of the skin and may be wiped off when a pronounced positive reaction warns of impending danger or when constitutional symptoms start to develop, is a decisive factor in diminishing the danger associated with the scratch test. It is not foolproof, however, and deaths have been reported as a result of its careless use. The clinician, when testing allergic patients, should therefore be on constant guard for signs or symptoms which may herald the approach or onset of systemic reactions.

Symptoms. Warning of an impending systemic reaction may be detected in certain phenomena associated with the cutaneous reaction itself or in various characteristic systemic symptoms and signs. At the site of the skin test, the cutaneous reaction may exhibit signs of excessive activity, such as the rapid and pronounced development of pseudopodia and the appearance of an unusually broad and intensive erythema. The pseudopodia frequently develop so rapidly that they appear to lose continuity with the body of the wheal. A thread-like line of edema or erythema may travel along a lymph channel for several centimeters above the wheal. Many new wheals, pinpoint in size, may appear around the primary wheal and fill the space between neighboring reactions. Other cutaneous reactions on the same arm or at more distant sites may suddenly begin to react with unusual rapidity and assume the explosive characteristics manifested by the marked primary reaction. Under the circumstances, neighboring wheals may fuse and form columns of edema surrounded by large expanses of erythema. All of these phenomena are usually accompanied by a marked degree of pruritus.

At any stage of development of the above phenomena and occasionally preceding them, systemic symptoms appear. They may include any or all of the following: (1) Severe pruritus at unusual cutaneous sites, such as the palms, soles, scalp, neck, auditory canals, anus, vagina or elsewhere on the body. (2) Sneezing and rhinorrhea. (3) Irritation of the nasopharynx or larynx causing a dry spasmodic cough. (4) Tightness in the chest and asthma. (5) Generalized or diffuse areas of erythema accompanied by a feeling of warmth. (6) Urticaria of variable distribution and intensity. (7) Angioneurotic edema or areas of diffuse edema which may become generalized.

Among the less characteristic symptoms of constitutional reactions are headache, vertigo, nausea and vomiting, abdominal pain, uterine contractions, tachycardia and others. Syncope is rarely an early manifestation of a systemic reaction and more frequently is psychic in origin.

Treatment. When it is recognized that a systemic reaction has developed or is impending, the situation demands immediate action. The successful control of the reaction depends almost entirely on the rapid administration of adequate doses of epinephrine. No other antidote will act so quickly and effectively. Hence, epinephrine and a sterile syringe for its administration should be immediately available whenever a skin test for sensitivity is being made.

When the test or injection has been made on an extremity, a rubber tourniquet may also aid in the prevention or the control of systemic reactions and should be at hand for immediate use. The tourniquet should be applied cephalad to the test site for the purpose of retarding the absorption of the allergen into the circulation. The epinephrine (1:1000) should be administered in amounts of 0.5 to 1.0 ml. or more. It should be injected subcutaneously above the tourniquet or anywhere on the body where rapid absorption may be obtained. Some epinephrine may also be given below the tourniquet deep into the site of the test or injection in order to induce local ischemia and to slow up still further, if possible, the absorption of allergen from the point of its deposit. Injections of epinephrine may be repeated several times in rapid succession if the situation is serious and a rapid and powerful action of the drug is urgently needed. The therapeutic dose of epinephrine, under such circumstances, may be considered that amount necessary to obtain the desired result. There are no contraindications to epinephrine at times like these, when the patient's life may be at stake. Even the intravenous administration of epinephrine should be resorted to in a crisis.

Once the constitutional reaction has been checked, one may administer sedation, if necessary, to counteract the stimulating effects of the epinephrine. In most instances, however, unless the reaction is unusually severe and heroic measures have been employed, the effects of the epinephrine soon wear off and no sedatives are needed.

Prevention. There are definite precautionary measures which should be taken routinely. Before any skin testing is attempted, a careful history of the patient's allergic background and of the nature and severity of his symptoms should be obtained. There should be careful questioning concerning any previous unusual experiences following exposure or contact with any inhalant, food, drug or other type of allergen. A history of severe clinical sensitivities should be respected and should be accepted as valid until such time as the facts may be checked by careful investigation.

In testing for hypersensitiveness, the existence of which is known or suspected from the patient's history, weak dilutions of the implicated allergen should be used. The routine testing strength of the extract usually considered "safe" for routine testing should be diluted ten or more times for the initial test, depending on the nature of the allergen and the clinical history. If negative reactions are obtained with these weak dilutions, stronger extracts may then be employed.

When testing with *potent* allergens (animal danders, seeds, fish, nuts, etc.) it is inadvisable to test with more than one member of a biologic group at a time. Even in the absence of a definite history of sensitivity, this practice is to be recommended as one of the best safeguards against constitutional reactions.

The patient should remain under the physician's immediate observation from the time the tests are introduced until they are read. The tests should be inspected at short intervals to make certain they are not developing too rapidly. Symptoms, such as coughing, sneezing, urticaria, unusual pruritus and flushing, should be noted immediately and their possible significance investigated, even when the patient does not complain about them.

Skin tests with drugs and chemicals should be avoided if possible. They rarely yield significant positive cutaneous reactions, but frequently cause severe constitutional reactions.

Finally, it is important to keep in mind that each case may present an unusual problem, and that no routine testing procedure may be regarded as safe under all circumstances. Sound practice calls for individualization in the testing of each patient, according to his age, the nature and severity of his symptoms, his history of sensitivities and the allergies which are likely to be encountered.

The Indirect Method of Testing (Passive Transfer)

There are times when, for one reason or another, it is difficult or impossible to perform skin tests on a patient. Rather than carry out this diagnostic procedure under unfavorable circumstances, or forego or postpone it indefinitely, it is advisable that the patient be tested by the indirect or passive transfer method. This technic, like the direct method, seeks to determine the presence of reagins in the patient's serum and tissues. However, it is a more technical and involved procedure than direct testing and requires considerable experience for its proper performance. The benefits to be derived from its use, nevertheless, justify the investment of the time and effort needed to master it.

Indications for Use. By resorting to the indirect method of testing, some of the difficulties which are encountered in the testing of patients may be avoided. Some of the commonest indications for its use include the following: (1) The presence of abnormal skin conditions, such as (*a*) urticaria, acute or chronic eczema or dermatitis; (*b*) impetigo or other contagious skin lesions; (*c*) ichthyosis, scleroderma, chronic pruritus and other conditions which produce toughening or scarring of the skin; (*d*) pronounced dermographism; (*e*) other diffuse chronic skin diseases. (2) The tendency to develop, after testing, many marked delayed skin reactions which are painful and interfere with subsequent testing in the affected areas. (3) The frequent or continuous use of epinephrine for the control of severe allergic symptoms. (4) The presence of unusually pronounced sensitivities in infants and children, which increase the danger of constitutional reactions from skin testing. (5) Reluctance on the part of parents or physician to submit a child to direct testing because of tender age, severe illness, incorrigibility or psychologic reasons. (6) Circumstances which prevent the patient from visiting his physician or from undergoing a satisfactory investigation of his sensitivities.

Technic. The technic for indirect testing which is being employed by Katherine Bowman and myself at the present time will be briefly summarized. Using a cool syringe moistened with physiologic saline, about 20 ml. of blood are drawn from the patient's vein under sterile precautions. The blood is transferred to sterile tubes and allowed to stand for a short time at room temperature. The clot is then rimmed and the tubes are placed in the refrigerator. The following day, the serum is removed and filtered (Seitz). After successfully passing sterility and Wassermann tests it is stored at 8° C. without preservative.

The substitute chosen for testing should be a normal, non-atopic, young adult preferably not a parent or close relative of the patient. He should show negative reactions to preliminary tests with common representative allergens (pollens, feathers, dust, wheat, etc.) and should possess a reactive but not hyperirritable skin. On the day of sensitization the substitute is placed on a diet excluding eggs, fish, fowl, nuts, peas, beans, mustard and any other foods for which the patient is known to have a marked clinical sensitivity. Experience has shown these foods to be the ones most likely to light up passively sensitized sites when, following ingestion, they are absorbed into the circulation. These local reactions are usually severe and render the sites useless for subsequent testing.

The substitute is sensitized by the intracutaneous injection of the patient's serum into a series of sites on both arms. About 0.03 to 0.05 ml. of serum is introduced as superficially as possible into the skin at each site. Four parallel transverse rows of from seven to twelve sites are prepared on each arm. All but the medial third of the circumference of the arm may be used. Each site is circumscribed with indelible pencil and the marks are renewed daily.

Testing of the sensitized site is usually postponed for five days to allow the skin to recover from the whealing and trauma resulting from sensitization. The tests are performed by the intracutaneous technic with about 0.01 to 0.02 ml. of allergenic extract, using the same dilution as for direct testing. Each test on a sensitized site is controlled by a similar one on adjacent normal skin. Alternate sites on alternate rows are used at the same sitting, from seven to ten being tested at one time. If no pronounced positives are obtained, another series of equal number may be tried on the other arm. The production of reactions of unusual intensity or of a multiplicity of strong positives at one time should be avoided, if possible, in order to prevent a "constitutional reaction" in the substitute. This phenomenon consists of a sudden uniform lighting up of *all* sensitized sites by allergens which enter the circulation from the points of their introduction at the sensitized and control sites. Except for the temporary discomfort resulting from the urticarial reactions on the arms, the substitute suffers no other systemic effects. The reaction, however, renders all the sensitized sites useless for further testing.

Sites on which no reactions are obtained may be used again for tests with other allergens after an interval of seven days. If a reaction of slight (one plus) or greater intensity is obtained at a sensitized site, further testing on that site should be avoided. A test giving a doubtful reaction should be repeated on another site with a more concentrated extract. When no reactions are obtained with important allergens in weak dilutions, stronger extracts may then be tried if test sites are available. Complete diagrammatic records should be kept of the time and nature of the tests made at each site and of the reactions obtained.

The results of the tests are read when the reactions have reached their height, which takes somewhat longer with this technic than with the direct method. In reading the reactions at the test and control sites, note is made of the size and intensity of the wheals and erythema.

Interpretation. Interpretation of the results obtained depends upon a comparison of the reactions elicited by each allergen at the sensitized and control sites. Any excess of wheal or erythema or both at the test site is considered a positive reaction and suggests the presence of skin-sensitizing antibodies to the test allergen in the patient's serum. While reactions at the sensitized and control sites may be read and recorded according to the standards employed in direct testing, evaluation of the result of the test depends less on the actual size of the reaction at the sensitized site than on the difference between this reaction and its control.

One occasionally finds a "*non-specific* sensitizing" substance in the patient's serum. This is particularly common in cases with atopic dermatitis and may be detected by testing a sensitized site with physiologic saline. If this yields a reaction in excess of its control, it is advisable to postpone further testing for a few days until this non-specific reactivity of the site diminishes or disappears. When this property of the serum is pronounced, it may be necessary to age the serum for a month or two in the ice box before it is tried again.

When a control reaction exceeds that on the sensitized site, the latter is probably refractory as a result of the skin trauma or inflammation produced by the sensitization procedure or by a previous test. The results obtained by the testing of refractory sites are not reliable.

A positive control test suggests either that the substitute is sensitive to that allergen or that the test extract is irritating. The former circumstance may seriously minimize the value of the investigation, since atopic persons accept sensitization less readily than normal persons.

Pruritus is not a reliable component of the reaction in indirect testing and should not be given the same consideration in evaluating the results of testing which the wheal and erythema receive.

A reaction obtained by the indirect method of testing indicates that reagins for that allergen are present in the patient's serum. This fact, as in the case of reactions in direct testing, is not proof of the patient's clinical sensitivity to that allergen, but is evidence which must be correlated with the patient's history and symptoms before it can be evaluated.

If the results of direct and indirect tests on the same patient are compared one usually finds that indirect testing has revealed no reactions which were unobtainable by direct testing. However, if direct tests are performed under unfavorable circumstances, as on old or abnormal skin, or with weak dilutions of extracts, while the indirect tests are done on a responsive skin or with strong extracts, the latter technic may, at times, appear to be more effective. On the other hand, it is possible to fail to transfer some true reactions with the indirect method when the reagin concentration of the serum is very low or an unsuitable substitute is used. The effectiveness of the technic, moreover, is directly proportional to the experience and skill of the technician who is performing it. However, any disadvantages of the indirect method are more than compensated for by the fact that *every test with this technic has an adequate control*, a feature which is lacking in direct testing with those extracts which are irritating to the skin.

The technic of indirect testing is, on the whole, a difficult one. It will reward those who master it, not only by serving as a substitute technic when direct testing is impractical but also by furnishing an insight into the theoretical aspects of skin testing which is unobtainable from the use of the direct method alone.

Relation of Positive Skin Tests to Clinical Allergy

Regardless of the technic of testing which is employed, all tests, positive and negative, need interpretation. A positive test does not necessarily indicate *clinical* sensitivity to the allergen which elicited it nor does a negative test exclude such a possibility. Attention has already been drawn to the fact that there are non-reaginic reactions which are of little significance in the diagnosis of atopic illnesses and that, even among reactions mediated by atopic reagins, there is a wide variation in clinical importance. Positive tests may precede, by many years, the onset of clinical hypersensitiveness to the allergens in question. Similarly, they may persist long after the symptoms of hypersensitiveness have disappeared. Moreover, there are reactions elicited by some allergens which seem never to play any role in the patient's allergic history. Since a reaginic reaction may be indicative of past, present or future sensitivity, the need for a careful clinical evaluation of each reaction is apparent.

Absence of reaction resulting from a test properly performed indicates the absence of reagins to the allergenic extract employed. It by no means rules out the possibility of a clinical sensitivity to that allergen. In drug sensitivity, negative skin tests are the rule. In disorders caused by food hypersensitiveness, negative tests to the offenders are, on the whole, more common than positive ones. Under the circumstances. negative tests, like positive ones, require evaluation.

Role of the Shock Tissue. One may speculate at considerable length as to the reasons why skin reactions do not parallel clinical sensitivity. All available evidence points to the fact that it is not the circulating reagins but those which become fixed in the "shock tissue" which mediate atopic symptoms as a result of union with the related allergens. The forces which control the behavior of these "shock tissues" and their responses to excitation are still unknown. It is significant that "shock tissues" may be activated not only by reaginic but also by non-reaginic immunologic mechanisms. Moreover. there is ample evidence that non-specific factors may also play a large part in their activation and inactivation.

Evidence of the independent role which the "shock tissue" plays in relation to symptoms is constantly encountered in the study of allergic disorders. In pollinosis, for example, almost every patient shows reactions to unrelated pollens for which he shows no clinical symptoms. In many allergic disorders, the functioning "shock tissue" is frequently inactivated, temporarily or for long periods of time, by an acute intercurrent illness, pregnancy, a fracture or a serious injury, while at the same time the skin reaction remains unchanged. A wide variety of different forms of non-specific therapy may accomplish the same result. In the light of such facts, it is apparent that the skin test or any other similar diagnostic procedure which fails to reveal any information concerning the state of the "shock tissue" is necessarily subject to serious limitations.

Reasons for Lack of Reactions to Foods and Drugs. There has also been considerable speculation as to the cause for the frequent absence of reactions in many types of food and drug sensitivity. A few of the possibilities which enter into this complex problem will be briefly mentioned. The active principles of certain food allergens, especially among the fruits and vegetables, are unstable and rapidly become inert in test extracts. In some instances, sensitivity to a split product rather than to the whole food may exist. Since the specificity of an antigen tends to change with its digestion, a test with an extract of a food in its natural state often fails to reveal sensitivity to derivatives of that allergen. There are, in addition, mechanical and technical factors, such as ineffective methods of preparation and preservation of allergenic extracts, or limitations in the testing technics, which may explain some of the inadequacies of testing with food allergens. Another important consideration is the fact that sensitizing mechanisms, other than that which involves the reaginic antibody, may excite the "shock tissue." This seems to be the case in sensitivity to aspirin, quinine and similar drugs, and it may be the same mechanism or a similar one which mediates some forms of food sensitivity in which negative skin reactions are obtained. The solution of these problems awaits further study.

Evaluation of Skin Reactions

For the proper evaluation of skin reactions, a knowledge of the various immunologic and non-immunologic factors which influence wheal formation is desirable. According to Thomas Lewis, the mechanism of the immunologic reaction in skin testing bears a close resemblance to that of the non-specific wheal reaction resulting from stroking the skin in dermographism or from the intracutaneous injection of histamine. According to Lewis, there is "triple response" of the skin to injury. This consists of "three mutually independent effects, which appear in the following order: (1) a primary and local dilatation of the minute vessels of the skin (arterioles, capillaries, venules) which were directly injured by the traumatic agent, (2) a widespread dilatation of the neighboring strong arterioles as a result of a local nervous reflex, (3) an increased permeability of the walls of the minute vessels which were directly injured by the stimulus." These separate phenomena are respectively responsible for the primary erythema, the secondary or surrounding erythema or areola, and the wheal formation which develops on the site of the primary erythema. Lewis postulates that the traumatized tissue cells liberate a "histamine-like substance" or "H-substance" which effects these changes. He suggests that, in skin testing, the union of allergen with the antibody fixed in the sensitized cell similarly results in a liberation of H-substance from the tissue cells. This liberation of H-substance initiates the triple response and produces the characteristic picture of the positive skin reaction. Although much of Lewis' work has been confirmed in subsequent investigations by other workers, suggestive evidence has been uncovered which implies, at least, some lack of complete identity in the mechanisms of non-specific and immunologic wheals.

Factors Influencing Degree of Reaction. There are many factors which influence the degree of cutaneous reaction in allergic illnesses. Some of the important specific factors have already been mentioned. They include reagin concentration in the blood and tissues and the amount of allergen employed. The latter factor depends upon the concentration of the test extract and upon the volume of solution injected.

There are, in addition, many important non-immunologic factors which affect the size of the cutaneous reaction. Perhaps the most important of these is the *state of the circulation*. Any force which impairs the flow of blood through the skin capillaries or vessels, whether the cause be general, as in syncope, shock or cardiac decompensation, or whether it be induced by local mechanical means, will diminish the size of the cutaneous reaction or even prevent it entirely.

The *region of the body* chosen as the site for skin testing will also influence the size of the reaction. With the same technic, larger specific skin reactions will be obtained on the back than on the arm or thigh, and these in turn will, as a rule, exceed in size the reactions obtained on the forearm and leg.

Skin reactions vary with the *age* of the patient. In the first year of life, the tendency to wheal formation is diminished and pseudopod formation is unusual. The erythematous part of the reaction is usually pronounced at this time. In the aged, there may be some diminution in the reactivity of the skin, particularly in the intensity of the secondary areola.

Other technical factors affecting the size of the skin reactions, such as irritability of extracts, the number of tests made at one time, their proximity to each other, the amount injected, the depth of the injection and the amount of trauma, have already been discussed.

A dose of *epinephrine* administered less than an hour before the performance of skin tests may diminish or prevent positive cutaneous reactions. It is questionable whether the drug continues to influence the results of testing after that period. Ephedrine taken orally and the use of epinephrine by inhalation produce only mild effects and in ordinary doses do not interfere with skin testing.

Delayed Reactions. Little is known of the significance of delayed reactions which may occur at the site of skin tests after periods varying from several hours to a day or more. The reactions are not mediated by a reaginic mechanism. They are usually red and indurated areas which may be extremely painful and may last several days. They may occur with a particular allergenic extract in many patients, indicating that some peculiar property of the preparation is responsible for this type of reaction. At other times, many delayed reactions may occur in one patient who manifests this tendency regardless of the nature of the extract employed. Delayed reactions may also occur early in the development of a sensitivity which is being artificially induced by repeated intracutaneous doses of animal serum or ascaris antigen. With the onset of reagin formation and the appearance of the immediate type of wheal reaction, the delayed reaction usually disappears. On the whole, delayed reactions are of doubtful diagnostic value and have not been found to afford reliable information concerning the patient's sensitivities in atopic disorders.

In addition to making a detailed study of each allergenic reaction, there is much to be gained by the clinician in seeking to obtain a broad view of the results of cutaneous testing in each patient. Recognition of the patient's predilections and potential sensitivities as disclosed by skin testing may be of considerable importance, especially in children, in the prevention of future allergic disorders. The judicious restriction or elimination of those types of food or inhalant contacts which skin testing reveals are potential, if not actual, offenders may help to prevent the development of new clinical sensitivities. This prophylactic phase in the management of allergic illnesses is one which has, in the past, received too little attention. Its importance, however, should not be overlooked by those who are interested not only in the immediate improvement but also in the future welfare of their patients.

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32. *Laboratory Procedures**

MARGARET B. STRAUSS AND W. C. SPAIN

The Purpose of Preparing Extracts

IN THIS attempt to provide information upon the preparation of allergenic extracts, it has seemed advisable to describe those procedures which have been chosen by the Allergy Laboratory of the New York Post-Graduate Hospital as being most useful. Many of these procedures have been changed but little since the early days of allergy when, in the New York Hospital laboratory, Cooke and Coca worked out the methods of the extraction of active antigenic material. Several methods have been devised in our own laboratory. It is of course realized that this is not the last word upon this subject and that new methods are certain to be introduced, but the fundamental procedures will probably remain unaltered.

The skin test, the outstanding specific diagnostic procedure in clinical allergy, whether performed by the scratch or by the intracutaneous method, represents an effort to utilize in a controlled, localized and wholly circumscribed way the general allergic mechanism which is activated when the sensitized person is thrown into contact with the specific exciting substance. In both cutaneous test and clincal reaction, the allergic antibody present in the tissues is exposed to an antigen of foreign origin, in the one instance in the vehicle of a prepared extract, in the other, in the clinical environment. Therefore, the more completely the antigen in extract form retains the characteristics which it possesses in its natural state in the environment, the more precise and the more accurate the cutaneous test will be. Indeed, it would be ideal if it were possible to perform the tests with the antigens in their natural fresh state or original condition. Since this manifestly is impossible, except in occasional instances, the attempt must be made to obtain a testing product which retains for considerable periods the antigenic characteristics of the raw materials.

Requirements for a Dependable Extract. It is relatively easy to prepare an extract with a high initial potency; it is more difficult to make one that will retain its activity after months of storage. To qualify as satisfactory therefore, an extract must not only contain the specific antigenic substance in active form; it must maintain a high level of potency over periods of months; it must be sterile; its pH must be adjusted so that it is non-irritating and painless when introduced into normal tissues; it must lend itself to standardization; and it must be in such a physical form, fluid or dry, that it can be utilized conveniently and without discomfort in the intracutaneous or in the scratch test. The following procedures have been devised with these prerequisites in mind.

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* The largest part of the material in this chapter has been adapted from A Manual of Procedures Used in the Allergy Laboratory of the New York Post-Graduate Medical School and Hospital.

Technic for Making Allergenic Extracts

1. **Collection and Storage of Antigens.** Extracts should be prepared from the raw, clean, unadulterated materials. Following is a list showing the form in which some of the antigens should be obtained. Pollens, carefully collected and immediately dried with silica gel[1] by the collector (then defatted and dried with ether and stored in the defatted state with silica gel or in vacuo); vacuum cleaner dust; chicken, duck and goose feathers in an unwashed, unsterilized state; dog, cat, rabbit, goat and horse hair; silk cocoons; orris powder; pyrethrum flowers; raw untreated sun-dried tobacco; cotton, kapok and flax seeds. Raw or untreated basic food materials should be procured as needed or when in season, such as meats; fish; fruits; vegetables; whole cereal grains; green coffee; tea; chocolate; spices; nuts. Prepared or processed foods (dried, frozen, canned, evaporated or chemically preserved) should not be used.

It is most important that the botanist collecting pollens take every precaution to keep the pollen dry at the time of collection and during any storage interval before it is sent to the laboratory. It is generally believed that moisture will quickly cause deterioration of fresh pollen, due most probably to hydrolysis of the protein or an active fraction in the pollen.

Berresford and Cooke[1] devised a machine which will dehydrate pollen to complete dryness in a few hours by passing warm, dry air continually over the pollen. The pollen should be dried immediately after collection in a drying apparatus of this type or by high vacuum to preserve the activity of the pollen even before it is defatted. Pollens should be defatted with ether as soon as possible after collection, dried at 50° C. in an incubator for two hours, then stored in sealed jars in the presence of silica gel, a highly efficient dehydrating agent. The silica gel* is conveniently placed into cellophane envelopes made from the regular cellophane sausage casing† which is $2\frac{1}{2}$ inches wide when flat. The ends are folded over once and secured with scotch tape. A cobalt moisture indicator is incorporated into the silica gel, imparting a deep blue color when the gel is free of moisture; a light pink color indicates maximum saturation of the gel with water. The moisture-saturated gel may be readily reclaimed by heating in a hot air oven. Pollen collected and sun-dried under the most careful conditions has been found to contain anywhere from 10 to 40 per cent moisture removable by successive changes of fresh silica gel. The defatted, dried pollen may again be placed in the warm air machine or dried with high vacuum before storage.

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* Kindly supplied through the courtesy of the Davison Chemical Co., Baltimore, Md.

† Visking Corp., New York City.

Feathers, animal danders and dusts must of necessity often be stored. These should be placed dry in glass or metal airtight containers in which silica gel has been utilized to keep the materials moisture-free.

2. **Preparation of Crude Material for Optimum Extraction.** (*a*) *Pulverizing or Grinding.* For optimum extraction, crude antigens, except pollens, should be reduced into as fine a particulate form as is practical. Dry materials such as grains and seeds are pulverized in a coffee grinder. Most bulky moist foods as meats, fish, vegetables, fruits, also nuts, tobacco and pyrethrum flowers are chopped finely in a meat grinder. From meats all visible traces of fat must be removed by hand before grinding.

(*b*) *Removal of Fats and Oils.* Preliminary to extraction, all antigenic materials except fruits and vegetables must be treated with an organic solvent to remove fats and oils. Stull and his co-authors[2] have shown that the skin test material is practically insoluble in ethyl ether, petroleum ether, chloroform or benzene.

Pollens are treated with ether, which has the disadvantages of being highly inflammable, very volatile and expensive. Anhydrous ethyl ether is added to the pollen in a large jar and mixed well. The pollen and ether are then transferred to a Buchner funnel and the ether is filtered off. (This ether fraction contains the pollen oil which is the causative agent of pollen dermatitis. The ether may be evaporated off and the pollen oil treated with absolute alcohol as described under alcoholic poison ivy extracts (p. 535) for the use in testing and treatment of pollen dermatitis.) The pollen remaining on the Buchner funnel is then washed with successive portions of fresh ether, directly on the funnel, until the ether washings are colorless. The filter is left on the suction outlet to permit air to pass through to drive off most of the ether before the pollen is transferred to an incubator set at 50° C. for drying.

All other materials, except meats, fish, nuts and fresh fruits and vegetables, may be extracted with toluene or with Sovasol #5,* both of which are less inflammable, moderately volatile and effectively prevent the growth of all bacteria and fungi in the aqueous solution if in sufficient contact with it. Carbon tetrachloride also has qualities similar to toluene, but is dangeous to use because of the toxicity of its vapors.

* A product of Standard Oil-Socony Vacuum Co., Brooklyn, N. Y.

Meats, fish and nuts, the fat having been cut away as much as possible from the meat, are ground and then treated with acetone, which is not only an efficient fat solvent but, in contrast to toluene and Sovasol, mixes in all proportions with water. This quality enables it to remove the water present in the muscle tissue of the meat or fish which otherwise would prevent adequate fat extraction by the organic solvent.

Regardless of the antigenic materials or the solvent used, several washings with fresh solvent are usually necessary before it remains colorless, which is evidence of fairly complete fat extraction. A Soxhlet type of extraction has never seemed necessary. The material is squeezed through several layers of gauze before fresh solvent is added to it. It is important to filter each portion of organic solvent used before it is discarded in order to reclaim any finely divided or powdery portion of antigen which otherwise might be lost. The acetone should be removed from the defatted material by thorough evaporation at room temperature before aqueous extraction is attempted. Pollens must be free of solvent and absolutely dry before aqueous extraction.

Other antigenic material to be extracted is completely covered with the organic solvent and is thoroughly mixed. Powdered or finely ground antigens may be stirred well at intervals and the colored solvent removed by decantation or filtration. Fresh solvent is then added, repeating the mixing, or the extraction may be continued overnight.

Feathers, dust and epithelia are extracted with Sovasol. Due to the greater bulk of these antigens a large quantity of organic solvent is necessary to cover them and they are allowed to stand, with occasional stirring, for two days in this fat extractive. The Sovasol is removed from the antigens by the use of a fruit press. It is very important to filter this Sovasol through filter paper before it is discarded. In this way a considerable quantity of valuable powdered antigen which was mechanically squeezed out with the Sovasol is retained on the filter paper and after filtration this residue is added to the large mass of antigen for the aqueous antigenic extraction.

3. **Extraction with Aqueous Extracting Fluids.** To prepare an extract with a high initial potency is simple, compared with the problems of preserving its activity over considerable periods of time. The addition of glycerin[3, 4] in large amounts (50 to 60 per cent) produces a relatively stable extract, but also one painful upon test and injection. Lesser amounts of glycerin (10 to 25 per cent) are no more efficient than are dilute ethyl alcohol,[5, 6] dextrose,[7] or saline,[8] all of which have been advocated. In the New York Post-Graduate Allergy Laboratory three extraction fluids are used, each selected for a different use. Extracts prepared with them do decrease in strength over a period of time but retain a satisfactory degree of potency for periods of eighteen to twenty-four months as evidenced by skin tests and clinical results. These

extraction agents are (1) alkaline extracting fluid (Coca[9]), (2) buffered saline extracting fluids (Evans),[10] in regular and concentrated (five-fold) forms, and (3) buffered sodium formaldehyde sulfoxylate extracting fluid (Strauss and Spain),[11] also in regular and concentrated (five-fold) forms. The extracting fluid used for each antigen is listed in Appendice 1, 2, 3 and 4, and if the volume of extracting fluid to be added to a special weight of antigen is important this is indicated. Regardless of the types of extracting fluid used, all antigenic material should, while being extracted, be covered with a layer of toluene or Sovasol to prevent evaporation and contamination from air-borne spores and bacteria.

For the preparation of a 50 per cent glycerinated extract which remains relatively stable, the following procedures may be used as outlined for the preparation of aqueous extracts except that one part of glycerin is added to one part of aqueous extract as the final step. This 50 per cent glycerinated extract is painful upon injection and will give positive reactions in skin testing due to the glycerin. Therefore glycerinated extracts must be greatly diluted before they may be used for skin testing and it should be noted that a 25 to 35 per cent glycerinated extract deteriorates at almost the same rate as an aqueous extract.

Pollens and dusts are extracted with alkaline extracting fluid (Coca), which has a *p*H of 8.2 and contains 0.5 per cent sodium chloride, 0.275 per cent sodium bicarbonate and 0.4 per cent phenol. Pollens are extracted for three hours at room temperature or overnight in the icebox. Dust is extracted for two days or more at room temperature.

All other materials, except juicy fruits and vegetables, are extracted with buffered saline or buffered sodium formaldehyde sulfoxylate extracting fluids.

Buffered saline is neutral, having a *p*H of 7.0, contains 0.4 per cent phenol, 0.5 per cent sodium chloride, and phosphate buffer sufficient to neutralize small additions of acid or base.

Buffered sodium formaldehyde sulfoxylate (hereafter referred to as S. F. S.) has a *p*H of 7.4 and contains 1 per cent sodium formaldehyde sulfoxylate and an acid phosphate-sodium hydroxide buffer.

For extraction of non-juicy material sufficient extracting fluid is added just to cover the antigen, which is extracted for two days at room temperature. The exact quantity of extracting fluid is not too important in most cases since the extract is standardized as a last step.

Juicy fruits and juicy vegetables are extracted with concentrated buffered saline or concentrated sodium formaldehyde sulfoxylate which are five-fold concentrations of the regular solutions. Since four parts of the fruit or vegetable juice are added to one part of concentrated extracting fluid, the final salt, phenol or sulfoxylate concentration in the juice is the same as that in the other dry antigens extracted with the regular extracting fluids. These juicy antigens are squeezed through gauze if there is any pulp present so that the liquid may be measured. After addition of the proper amount of concentrated extracting fluid this pulp is extracted with the juice and extracting fluid. Many of these fruit and vegetable juices contain such an excessive amount of acid that they would immediately over-ride the buffer capacity of the extracting fluid. It has, therefore, been found useful to add concentrated (1:1) sodium hydroxide solution (see Appendix 5) until the juice is neutral before adding the calculated amount of concentrated extracting fluid. Tuft[12] has suggested immediate neutralization of fresh fruits and vegetables to preserve their potency.

Buffered sodium formaldehyde sulfoxylate solutions described by Strauss and Spain are used to extract many fruits, vegetables, seeds and grains which, though light-colored themselves, give rise to very darkly colored or black extracts if any of the other previously mentioned extracting fluids are employed. Such dark extracts are undesirable since they tend to leave pigment fixed in the skin at the site of the test. Sodium formaldehyde sulfoxylate, a strong reducing agent, prevents the formation of these darkly colored oxidative pigments. The table in Appendix 4 gives a list of antigens which would give very dark-colored extracts if S. F. S. extracting fluid was not used.

4. Separation and Filtration of Extract from Antigen Mass. After extraction with aqueous extracting fluid, the main bulk of original antigen is removed from the aqueous extract. There are three modes of filtration; the method used in each case is the one best adapted to handle the physical characteristics of the material. All bulky material is first squeezed through gauze either by hand or by means of a fruit press before filtration through paper.

(*a*) The simplest method of filtration is through coarse filter paper which has been fluted to increase the surface and thus the speed of filtration. Dusts, fruits (with exception noted below), vegetables, meats, fish, epithelia, silk, tobacco and other bulky materials are treated in this manner.

(*b*) Filtration through a Buchner funnel with suction is a second method which is convenient and speedy for the filtration of powdered or finely granular substances. Mixtures which are gummy, sticky or emulsified will not filter well on a Buchner since the suction will pack a fine layer of the material on the filter paper which will tend to block further filtration. Pollens, spices, nuts, chocolate, coffee and other powdered extracts are filtered on a Buchner funnel.

(*c*) A cotton filter is almost indispensable in filtering extracts which have a jelly-like consistency and which will filter through filter paper only very slowly if at all. A piece of absorbent cotton, approximately 2 inches square and one-half the thickness of that found in the ordinary roll, is moistened and the excess water squeezed out. The cotton pad is then placed on the bottom of a large-sized glass funnel surrounding the opening to the stem and is firmly patted all around the sides of the funnel. Orris root, apricot, peach, apple, banana, seeds, grains and all other extracts of an emulsified or jelly-like consistency are filtered through a moist cotton filter.

5. **Dialysis of Extracts.** All extracts are dialyzed except the pollen, milk, egg and horse serum extracts. #600 cellophane sausage tubing ($2\frac{1}{2}$ inches wide when flat) is the semipermeable membrane used for dialysis. This grade of cellophane is well suited for this purpose since it retains the larger protein molecules with which the activity of the extract is associated, allowing the electrolytes, a large amount of coloring matter and lower molecular non-specific irritating substances to dialyze out. Many extracts have over-run the buffer capacity of the extracting fluid during extraction and are acid or alkaline. Dialysis is continued until all extracts are neutral since acid or alkaline extracts would tend to give false positive skin tests.

Procedure. A suitable length of cellophane tubing is cut from the roll. In order to separate the sides which tend to stick together the tubing is placed under the tap water and the cellophane is thus softened. Open the top edge with a pointed instrument and allow a stream of water to run through which separates the sides. At one end of the tubing a double fold is made which is pleated together and tied securely with string. The extract is introduced into the casing from the other end and a thin layer of toluene is added to check bacterial contamination. The sides of the casing above the liquid are then flattened together with the fingers displacing most of the air. This end of the casing is then sealed in the same way as the other end. The casing is placed in a fairly large-sized jar which is filled with buffered saline or buffered S. F. S. The extracts which were extracted with buffered S. F. S. extracting fluids are dialyzed against buffered S. F. S. *p*H 7.4. All other extracts are dialyzed against buffered saline. The buffered saline or S. F. S. is changed every twenty-four hours until its original *p*H is maintained after a twenty-four hour period of dialysis. The *p*H is checked by the use of Squibb's nitrazine indicator paper which changes colors at various *p*H ranges.

6. **Concentration of Extracts.** Some extracts, before use, must be concentrated in order to obtain satisfactory testing and treating strengths. These are the fruits, vegetables, epithelia and dusts. Pollens, meats, fish, nuts, seeds and grains need not be concentrated. After dialysis is completed, the extract is filtered if any large amount of precipitate has appeared. The filtered extract is replaced in the cellophane casing and a layer of toluene or Sovasol is added. The filled tubing is then hung from a line before an electric fan. The extract may be concentrated to any desired volume by evaporation through the membrane. Extracts are also concentrated at a much faster rate by the use of silica

gel. The extract is placed in cellophane tubing and layered with toluene as above. It is then placed in a large glass jar and completely surrounded by silica gel. After an hour or so one can observe from the color change that the gel in the immediate vicinity of the tubing has become saturated with water. The jar should then be carefully shaken or the gel redistributed with a spoon so that fresh active gel is in contact with the casing. By handling in this way it is possible to concentrate extracts four to six-fold in eight hours. This is much faster than concentrating by evaporation in the air. The extracts are usually filtered after concentration since precipitates generally form during this procedure.

7. **Sterilization of Extracts.** After the preliminary filtration of an extract, to separate it from the mass of crude material, with subsequent dialysis, concentration and ordinary paper filtration where indicated, the *p*H of the extract is again checked to make certain that it is neutral. Dilute NaOH solution is added until a *p*H of 7.0 is reached if the extract is acid. The next step is to insure freedom of the product from bacterial or fungi contamination. Sterilization by the addition of chemicals is undesirable since non-specific irritation may result from them. The use of heat is contraindicated since it destroys the antigenic activity. Sterilization by the mechanical removal of contaminants, that is, bacterial filtration, is necessary.

There are two types of bacterial filters in general use, the Seitz* and Berkefeld filters. The Seitz filter is the one recommended since its filtering surface consists of a special type of asbestos pad which is discarded after one filtration and which is inexpensive to replace. The two metal parts of the Seitz filter are washed with a soft cloth and mild soap, rinsed well and dried. A piece of regular filter paper is placed beneath the asbestos pad when it is assembled for sterilization to prevent lint from the asbestos from passing into the extract.

The Berkefeld filter consists of a tall narrow thimble of diatomaceous earth, the bottom of which is sealed to the metal end of a funnel. These cylinders must be carefully handled as they crack easily and after use must be brushed to remove scum, boiled for thirty minutes in 1 per cent $NaHCO_3$, then boiled for thirty minutes in 1 per cent HCl and finally boiled for thirty minutes in six changes of distilled water. Then approximately 500 ml. of distilled water are drawn through the candle before sterilization. These filters are expensive and fragile and have been discontinued from use by this laboratory.

A definite quantity of extract is absorbed by the asbestos pad of the Seitz filter, not only in terms of volume of extract but some of the activity is also removed, even if the pad is moistened by a preliminary filtration of buffered saline. It is therefore advisable to use a smaller size filtering cup and pad when smaller quantities of extracts are filtered to reduce proportionally the amount of activity which is lost by adsorption. The 100 ml. and 25 ml. Seitz filter cups have been found adequate to cover most cases.

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* Allergists Supply Co., New York City.

When very small quantities of extracts (2 to 15 ml.) need bacterial filtration (especially in the office when there is any question of a contamination due to the presence of a cloudy extract) a micro type of Seitz filter is more opportune. This type of filter is on the market as a "*Swinny Filter Adapter.*"* The asbestos pad of this filter is ½ inch in diameter in contrast to the 1⅜ inch and 2⅜ inch diameter of the 25 and 100 ml. cup filters. Obviously, this smaller pad with greatly reduced surface will absorb less extract and small quantities of solutions may be sterilized with no appreciable loss in volume. This micro type filter requires pressure in filtering the liquid in contrast to the larger Seitz and Berkefeld filters which use suction to draw the liquid through. A Luer-Lok syringe, used to hold the solution to be filtered, is locked onto the end of the sterile Swinny Filter Adapter and by pressure from the hand on the piston the solution is forced through the adapter into a sterile vial. A (10 ml.) three ring Luer-Lok* has been found to be a convenient size and much easier to manipulate and apply pressure to than the regular Luer-Lok syringe.

Extracts must be kept at ice-box temperature except when in use since they deteriorate at a much greater rate at room temperature. Formerly all extracts were stored in brown bottles but it is now believed that oxidation does not contribute appreciably to the deterioration of these extracts.

Procedure for Bacterial Filtration. When the Seitz filter is assembled preparatory to sterilization, the side arm of the filter flask is plugged with cotton. This side arm and the junction between the flask and rubber cork holding the Seitz filter are completely covered with several layers of clean cloth.

The wrapper is removed from the sterile Seitz filter or simply slipped over the side arm and allowed to remain over the junction of flask and stopper to keep this sterile. The rubber stopper is pressed firmly into the neck of the flask, care being taken to handle only the top of the stopper and not the rim of the flask. Next, the cup is screwed to the lower metal filter as tightly as possible. If there is a layer of toluene over the extract, the latter is pipetted out from under the toluene into the Seitz cup.

No toluene should be carried over into the Seitz or Berkefeld filters. After the extract has been in the Seitz cup for one or two minutes, the cup is again tightened to the funnel. This step is very important since the asbestos pad shrinks on wetting and the extract would leak through the base joint instead of filtering through the pad were the filter not retightened. The suction is then turned on. This same general procedure must also be followed with the Swinny Adapter. A slight pressure on the syringe will force a few drops of liquid onto the pad. The adapter must then be retightened as even this small pad shrinks appreciably when wet. The same general procedure is followed in using the Berkefeld candle except that here care must be taken to tighten the rubber washers which secure the glass cup onto the filtering candle. This must be done before any extract is placed into the glass cup.

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* Becton, Dickinson & Co., Rutherford, N. J.

After filtration has been completed, the extract is transferred, in a sterile room, from the filter flasks by means of sterile 50 or 100 ml. pipets into sterile containers, 4 to 8 ounce Pyrex nursing bottles, the type with a small neck being useful for these extracts. These bottles have a number of advantages. They are made from Pyrex glass, are sturdy, inexpensive, easily cleaned and sterilized, store in a minimum of space, and are roughly graduated in ounces. The neck of the filled bottle is flamed, closed with a sterile #0 rubber stopper which is flamed and the stopper and neck then covered with a hood of vegetable parchment ("Patapar") and tied snugly around the neck of the bottle. For all hooding or wrapping requirements in the laboratory, vegetable parchment is preferable to heavy paper or muslin since it is more durable, non-absorbent, may be reused, and sheds no lint. After proper labeling, the extract is held at room temperature for twenty-four hours before samples are taken for cultures, after which the extracts are stored in the refrigerator.

8. **Tests for Sterility.** The Seitz (or Berkefeld) filtration procedure removes a certain amount of antigenic activity from an extract. Therefore, before any attempt at standardization of potency is made sterility should be confirmed, as any refiltration made necessary by contamination through imperfect original filtration or improper bottling would again change the activity of the extract. Tests for sterility are made twenty-four hours after the extracts are bottled, both aerobic and anaerobic cultures being necessary.

From 0.2 to 0.5 ml. of the extract is transferred with a sterile pipet to a plain clear broth aerobic culture tube and a chopped meat clear broth anaerobic culture tube. The anaerobic culture is important since it is possible that pollens, epithelia and grains could carry spores along with them if improperly filtered. The cultures are incubated at 37° C. for forty-eight hours and the anaerobic tubes for two days longer. A positive culture is indicated by a cloudy media and the presence of gas beneath the petrolatum seal of the anaerobic tube. The extract must then be refiltered through a Seitz or Berkefeld filter.

More recently, a thioglycollate medium[13] has been introduced for both aerobic and anaerobic culture. The complete medium is obtainable in powdered form* and need only be dissolved in water and sterilized. It is much easier to handle than other types of anaerobic media since it needs no seal or special tubes and has been highly recommended by many bacteriologists. When thioglycollate media alone is used for cultturing, duplicate cultures are made using different sterile pipets for each culture.

9. **Standardization of Extracts.** Even with the most careful and most advanced procedures available, the degree of specific potency of an extract can only be approximated This is due to the fact that it has, so far, been impossible to evaluate directly and conveniently the specific exciting substance itself. It has been necessary to use as indices of potency the measurements of factors which are closely related to, but not identical with, the active substance, and which lend themselves to quantitative determination. One of the earliest attempts at standardization, and one still employed in some quarters, is that proposed by Noon,[15] based upon the weight of the material before extraction. Such weight by volume standardization is simple but not reliable since it does not take into consideration the important fact that varying amounts of activity can be extracted from the same material under different conditions and that the actual amount of active material in pollen varies seasonally under different conditions of plant growth. Furthermore, improperly stored pollen loses activity while retaining its weight. The ratio between weight and activity is variable, which outweighs in importance the ease and convenience of this method of standardization.

It was found by Cooke[16, 17] that a dependable ratio, particularly in freshly made extracts, existed between the activity and the total nitrogen content, although it was realized that these factors were not identical. The designation of potency was based upon the number of milligrams of total N contained in each milliliter of extract. This method was used for years in many clinics including ours, as the most reliable, even though it was apparent that stored extracts, although decreasing in potency, did not lose a corresponding amount of total N, but retained their original N content, a highly unsatisfactory situation when fresh and stored extracts were interchanged.

It was found eventually by Cooke and Stull[18, 19] that while aging did not affect the total N of an extract, it did influence greatly the fractions involved, the protein N and the non-protein N, the former being converted gradually into the latter, and that as this occurred a corresponding loss in activity was evident. A standard, then, based upon the protein N content rather than on the total N content was more pertinent and accurate.

Cooke and Stull suggested the protein nitrogen standard for allergen extracts since the activity of an extract was usually found in the protein fraction,* the non-protein fraction being considerably less active. The protein nitrogen standard is particularly helpful when changing from one year's pollen extract to another since it is a more accurate measure of the true activity than the total nitrogen. Another advantage of the protein nitrogen standard is shown in the following example: suppose that a 1945 pollen extract had a total nitrogen of 0.50 mg. per milliliter and a protein nitrogen of 0.25 mg. per milliliter, and the 1946 extract had the identical total nitrogen of 0.50 mg. per milliliter but a protein nitrogen of 0.15 mg. per milliliter, these pollens being extracted at the same time. These two extracts would seem to be of equal strength if judged solely on the total nitrogen standard but if they were diluted to the same total N strengths, the 1945 extract would be more reactive than the 1946 extract. If, however, these extracts were diluted to the same protein nitrogen strengths, both extracts would give identical reactions, showing that the protein nitrogen is the more accurate standard for the activity of the extract.

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* Baltimore Biological Laboratory, Baltimore, Md.

Although the ideal method for standardization has yet to be developed, most reliable so far, hence adopted in the Post-Graduate Hospital Allergy Clinic, is the estimate of the protein nitrogen content. One unit of activity established by Cooke and Stull contains 0.000,01 mg. of protein nitrogen per milliliter, and roughly about 0.000,024 mg. of total nitrogen per milliliter.

Since numerous standards for allergic extracts are in use, it may be helpful to be able to approximate the relative strength of one standard in terms of the others. These comparative values may be ascertained as follows:

In this laboratory, pollen extracts are made in the proportion of 4 to 8 grams of pollen to 100 ml. of extracting fluid and the resultant extract has usually an average strength of 2,000,000 units in 100 ml., the total strength obtained from 4 grams of pollen.

2,000,000 ÷ 4 = 500,000 units, the strength obtained from 1 gram of (ragweed) pollen

or 500 units, the strength obtained from 1 mg. of pollen.

Noon's pollen unit is the amount of extract obtained from 0.000,001 gm. or 0.001 mg. of pollen. Since 1 mg. pollen gives 500 units (P.N.), 0.001 mg. or 1 Noon unit gives 500×0.001 or 0.50 units (P.N.).

Experience has shown that the protein nitrogen averages about 40 per cent of the total nitrogen or, in other words, the total nitrogen is 2.5 times as great as the protein nitrogen. Hence: 1 unit (Cooke) of extract (0.000,001 mg. P.N.) contains about 0.000,025 mg. total N.

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* That the allergen of the pollen extract is protein, or at least some component of the protein molecule, is evidenced by the fact that a purified protein substance extracted from pollen will completely neutralize (passive transfer) the skin-sensitizing antibodies in appropriate serums obtained from pollen-sensitive patients. It is further supported by the fact that the blocking or neutralizing antibody in the serum of treated patients is likewise specific for the purified protein from the pollens. (R.A.C.)

Using the weight by volume standardization, a 1:100 solution means that each milliliter contains 0.01 gm. of dry pollen and a 1:1,000,000 solution means that each milliliter contains 0.001 mg. of dry pollen.

STANDARDS OF EXTRACTS

Noon Unit: Based on original pollen weight
1 Noon Unit = 1/1,000,000 gram or 0.001 mg. pollen
(Also called a pollen unit)

Cooke Unit: Based on protein nitrogen content or extract
1 Cooke Unit = 0.000,01 mg. protein nitrogen per milliliter

Total Nitrogen Unit: Based on total nitrogen content of extract
1 total nitrogen unit = 0.000,01 mg. total nitrogen per milliliter
(Also called a pollen unit)

Dilution Standard: Based on a weight by volume extraction and dilution
A 1:100 extract contains 0.01 gram of extracted pollen per milliliter

SUMMARY ON APPROXIMATE EQUIVALENCE OF VARIOUS UNITS

0.001 mg. of extracted pollen is contained in
1 ml. of a 1:1,000,000 dilution extract, *or*
1 Noon unit, *or*
0.50 P.N. units (Cooke), *or*
0.000,013 mg. total nitrogen, *or*
1.3 Total nitrogen units

Therefore, 1 P.N. unit (Cooke) = 2 Noon units = 0.000,026 mg. total nitrogen = 2.6 total nitrogen units = 1:500,000 dilution extract (pollen weight by volume).

All extracts except dust are standardized on a protein nitrogen basis. Dust is not standardized on a nitrogen basis but by a straight dilution of the original material if necessary.

In treatment with the inhalant extracts, strengths of 10; 100; 500; 2000; 5000; 10,000; and 20,000 units are available; the last three strengths are to be employed with considerable caution due to their activity.

10. **The Nitrogen Estimation.** (*a*) *Separation of Protein and Non-protein Fractions for Standardization.* It is first necessary to separate the total nitrogen of an extract into its protein and non-protein fractions in order to estimate the former. Samples are obtained of from 3 to 5 ml. of such foods as meats, fish and nuts, high in protein nitrogen, and from 10 to 20 ml. of the remaining foods and inhalants. Lesser amounts do not contain sufficient nitrogen to come within the limit of error of the macro Kjeldahl nitrogen method. All determinations are run in duplicate and must check to within 0.01 ml. of 1/14 N acid solution.

Concentrated hydrochloric acid and phosphotungstic acid solution are added to the sample, which is allowed to stand for one hour; centrifugation packs the precipitate, which is the protein nitrogen fraction, leaving the non-protein fraction in the supernatant fluid; the two fractions are then separated.

The nitrogen determination is made directly upon the protein fraction.

Those who continue to use the total nitrogen content for standardization make the nitrogen determination directly on the whole extract without carrying out any separation.

PROCEDURE. (in detail). Clean, dry, non-sterile, accurate volumetric pipets are used to measure the extract for the nitrogen determination in contrast to the ordinary sterile 10 ml. graduated pipets for bacteriologic use. It is, therefore, necessary to pour the approximate quantity of sterile extract needed for the determination into clean, dry 10 ml. vials so as not to contaminate the stock extract by the introduction of the non-sterile volumetric pipet.

For the total nitrogen determination the appropriate quantity of extract is accurately pipeted directly into a clean Kjeldahl flask and the procedure described under the heading for the Kjeldahl determination is followed.

SEPARATION OF THE PROTEIN NITROGEN FRACTION. To 10 ml. of extract, transferred with a clean, dry volumetric pipet into a test tube (6×1 inch), there is added 2.5 ml. of concentrated HCl and 1 ml. of phosphotungstic acid solution and the contents of the tube are mixed thoroughly by rotating by hand. If 20 ml. of extract are used, a double quantity of each of the above two reagents is necessary. Allow the mixture to stand for one hour and then centrifuge for five to ten minutes at a fairly high speed to pack the protein precipitate. Pour off the supernatant fluid (non-protein fraction).

Phosphotungstic acid wash solution (see Appendix 5) is added to the protein precipitate from a wash bottle, washing down the sides of the test tube in the process, and a clean glass rod is used to mix the precipitate and acid wash solution. Before removal of the rod it is carefully washed with the acid wash solution allowing all of the washings to be caught in the test tube. The tube is again centrifuged and the supernatant is poured off. (If a nitrogen determination is desired on the non-protein fraction, the above two supernatants are collected in a Kjeldahl flask. This is the complete non-protein fraction, and if its nitrogen value is added to that of the protein fraction, the total nitrogen is obtained.)

The protein precipitate in the test tube is dissolved by the addition of 5 ml. of 2 per cent sodium hydroxide solution which should be dropped down the sides of the tube to dissolve any precipitate clinging there. A glass rod is introduced to help break up and dissolve the protein. The test tube is then three-quarters filled with distilled water and the solution is carefully transferred to a clean Kjeldahl flask. The test tube is rinsed three times with distilled water, each washing being added to the protein fraction in the Kjeldahl flask.

(*b*) *Macro Kjeldahl Nitrogen Determination in Detail.* Kjeldahl's original procedure devised in 1883 for the determination of nitrogen has been revised to insure and accelerate complete digestion. The first step in the method is the digestion of the material with an acid digestion mixture containing sulfuric acid which changes all of the nitrogen (organic or inorganic) to ammonium sulfate. Phosphoric acid is added to this acid digestion mixture to raise the boiling point; copper sulfate acts as a catalyst. Glass beads are placed into the flask to avoid excessive bumping. The digestion should be carried out under a hood or, if this is not available, the sulfuric acid vapors must be carried off by suction. A manifold is easily devised which removes the fumes from a whole series of flasks at the same time, drawing them off by means of suction through a strong sodium hydroxide solution for absorption of acid fumes.

The second step is the distillation. The still consists of a metal bath with a continuous flow which cools a series of lead tubes. Each of these at the upper end is connected by rubber tubing to a glass tube which passes into the neck of the Kjeldahl flask by means of a tightly fitting rubber stopper. The glass tubes contain a safety bulb which prevents any alkali from spattering into the condenser and being drawn into the standard acid. The lead tubes leading out of the lower end of the condenser are connected by rubber tubing to glass tubes, the lower ends of which dip into the receiving bottle containing the standard acid. The ammonium sulfate is rendered alkaline, liberating the ammonia which is then distilled and caught in the standard acid. This standard acid is then titrated against a standard alkali and the difference between the amount of acid originally placed in the receiving flask and the amount of alkali needed for its neutralization represents the amount of acid bound by the ammonia.

PROCEDURE. (1) *Digestion.* The material is placed in an 800 ml. Pyrex Kjeldahl flask to which are added 20 ml. of acid digestion mixture, (Appendix 5), 3 ml. of 10 per cent ferric chloride solution and 3 to 4 glass beads. A glass connecting bulb is placed in the mouth of the Kjeldahl flask. If the digestion cannot be carried out under a hood, secure the connecting bulb to the flask by means of Gooch crucible rubber tubing (1¾ inches wide when flat). This prevents the escape of acid fumes into the room. The flask and connecting bulb are attached to the suction-manifold and placed on the electric hot plate.

First the water present is boiled off and then dense white fumes fill the flask. The oxidation of the organic matter takes place as evidenced by the charring. Boiling is continued until the solution has become clear. The flask is allowed to cool and the contents are then diluted with approximately 200 ml. of distilled water and mixed well. If desirable, the procedure may be delayed at this time.

(2) *Distillation.* First the 1/14 N acid (Appendix 5) (15 ml.) and 13 drops of methyl red-methylene blue indicator are carefully measured into the receiving bottle. Distilled water is added so that the solution has a depth of approximately 1½ inches. The connecting tube from the bottom

of the condenser is then placed in the acid of the receiving bottle. Water is turned on to cool the condenser.

The Kjeldahl flask containing the digest, diluted with 200 ml. of water, is tilted so that the neck of the flask is at an angle. Approximately 50 ml. of concentrated sodium hydroxide solution are run in along the side of the flask with care so that the alkali runs down and forms a separate layer under the acid solution and does not mix with it. The upper acid layer serves to prevent the escape of any ammonia. 50 ml. of concentrated NaOH are enough in excess of the amount necessary to neutralize the acid from the digestion mixture so as to always make the digest distinctly alkaline.

The electric hot plate is then turned on. The flask is connected to the still without mixing its contents. After a tight connection is made, the contents of the flask are mixed by a whirling motion of the flask and the latter is then clamped into place over the hot plate. Distillation is continued until three fourths of the solution has boiled away or until bumping starts.

Before the heat is turned off it is very important to wash the outside of the delivery tube with distilled water into the receiving bottle and allow it to rest on the top of the bottle in such a manner that a few milliliters of distillate will run down the inside of the delivery tube and into the receiving flask, thus rinsing out the inside of the tube. After the boiling has continued for a few minutes the heat is turned off. If the heat is turned off before the delivery tube is removed from the acid in the receiving bottle, the acid may suck back into the distilling flask and the determination will be lost.

(3) *Titration.* The deep purple colored acid solution is titrated against 1/14 N sodium hydroxide solution to an emerald green color.

(4) *Calculations.* One milligram atom, or 14 mg. of ammonia nitrogen, is titrated by one milligram equivalent, or 1 ml. of 1 N acid. Therefore, the number of milliliters of 1 N acid neutralized by the ammonia is multiplied by 14 to calculate milligrams of nitrogen. By employing 1/14 normal acid no multiplication is necessary since every milliliter of 1/14 N acid used is equivalent to one milligram of nitrogen.

At frequent intervals blank determinations must be run on the reagents alone. The blank generally uses between 0.05 and 0.10 ml. of 1/14 N acid.

A = ml. of 1/14 N acid placed in receiving flask (15 ml.).

B = ml. of 1/14 N alkali required to titrate the excess of acid not used by the ammonia.

C = ml. of A − B found in blank analysis of reagents (0.10 ml.).

Since every milliliter of 1/14 N acid used is equivalent to 1 mg. of nitrogen, the milligrams N in sample analyzed = A − B − C.

Example:

(A)	15.00 ml.	1/14 N HCl in receiving flask
(B)	−12.48 ml.	1/14 N NaOH titrated to neutralize excess acid
	2.52 ml.	1/14 N HCl used up
(C)	− .10 ml.	1/14 N HCl used up by reagents alone
	2.42 ml.	1/14 N HCl used up by ammonia

2.42 mg. nitrogen in sample analyzed

2.42 ÷ 10 (volume in ml. of sample analyzed) = 0.242 nitrogen per milliliter material analyzed.

If the above were from a protein fraction, the 0.242 mg. would be protein nitrogen or 24,200 units.

11. **Dilution to Testing and Treating Strengths.** By making the necessary substitutions in the following equation, it is very easy to calculate the quantity of concentrated extract necessary for any desired volume or concentration of an extract.

Concentration of A × volume of A = concentration of B × volume of B. Let A represent the concentrated extract of a known total nitrogen or unit strength and B is the extract of testing or treating strength which is desired. If, for example, an orange extract has a total nitrogen (T.N.) of 0.23, and 10 ml. of a 0.05 T.N. is desired, the following substitutions are made:

Concentration of A × volume of A = concentration of B × volume of B

$$.23 \times X = .05 \times 10$$
$$X = 2.17 \text{ ml.}$$

Therefore, 2.17 ml. of the 0.23 T.N. concentration of orange extract is made up to 10 ml. or 7.83 ml. (10−2.17 = 7.83) of buffered saline is added to 2.17 of concentrated orange extract to give 10 ml. of 0.05 T.N.

Likewise, if a ragweed extract had a concentration of 18,500 units and 100 ml. of 5000 units were desired, the following calculations are made:

Concentration of A × volume of A = concentration of B × volume of B

$$18{,}000 \times X = 5000 \times 100$$
$$X = 27.0 \text{ ml.}$$

Therefore, 27.0 ml. of the 18,500 unit extract is made up to 100 ml. or 73.0 ml. (100 − 27.0 = 73.0) of buffered saline is added to 27.0 ml. of the 18,500 unit extract to give 100 ml. of 5000 units.

Miscellaneous Extracts

1. **Milk.** Milk extracts are usually made of the lactalbumin fraction since the casein fraction rarely is important as an excitant. Rennin added to fat-free milk curdles the casein by its enzymatic action and permits separation of the clear fluid known as whey, which contains the albumin.[20]

Procedure. To 800 ml. of fat-free milk is added 2.5 ml. of 1 per cent rennin. The mixture is placed in a water bath or incubator at 37° C. for thirty minutes without stirring. The clabber which contains the casein separates out and is poured, not squeezed, through a clean towel and the whey is collected and then filtered through filter paper. To this filtrate which contains the lactalbumin are added 8 ml. of a saturated solution of sodium bicarbonate and then buffered saline to make a 1:2 dilution of the whey. This is then Seitz-filtered and standardized after sterility tests are complete.

2. **Egg White.** It is possible with careful technic to collect egg white from fresh eggs under sterile conditions so that filtration through a Seitz or Berkefeld filter is unnecessary. The shell is washed well with 70 per cent alcohol. The shell is then either tapped with a sterile syringe and the egg white transferred to a sterile bottle or the egg may be cracked over the lip of a wide mouthed sterile flask and the egg white allowed to run into the sterile flask, the yolk being held back in the shell. If the latter technic is used it is important that the fingers do not touch the egg shell along the cracked surface over which the white may run. A 1:10 dilution of the egg white with sterile buffered saline is stored as the stock extract. If advisable, this may be Seitz filtered. After sterility tests are completed the nitrogen strength of the extract is determined.

3. **Horse Serum.** A 1:10 dilution of sterile horse serum with sterile buffered saline is stored as the stock extract. After sterility tests are completed the protein nitrogen strength of the extract may be determined although simple saline dilutions prove adequate for test purposes.

Preparation of Mold Extracts

A medium which will support the growth of various fungi contains 2 per cent maltose, 2 per cent crude dextrose and 1 per cent peptone in tap water. The mixture is boiled and placed in penicillin culture flasks. Adjustment of the *p*H is not necessary since the *p*H is sufficiently acid (5.5 to 6). The medium is sterilized by autoclaving at 15 pounds pressure for twenty minutes. Penicillin culture bottles* are most convenient and economical for use in growing the various fungi. They are 2 inches high when placed on their sides and may be stacked one on top of another when in use. A surface of approximately 4 by 10 inches is available for mat growth with only 200 ml. of media necessary for each flask. A much larger volume of media is needed for this size mat in a regular 2 liter Erlenmeyer flask and more storage space is also necessary.

Pure cultures of various fungi may be purchased from the American Type Culture Collection.†

Cultures are readily identified from growths in an agar petri dish. Examination is made under the high power of a microscope by removing the lid of the petri dish and placing the lower part directly under the microscope and focusing at the outermost edge of young colonies. In this way the culture is examined without distortion due to crushing or tearing caused by placing onto a slide.

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* Eimer & Amend, New York.

† Georgetown University School of Medicine, Washington, D.C.

A pure culture of the desired mold is inoculated into the broth and is allowed to grow at room temperature since the optimum temperature for cultivation is 20 to 25° C. A period of two to three weeks is generally required for the formation of a thick fungous mat completely covering the surface of the medium. After growth is of sufficient size, the medium is decanted and discarded. The mat is washed once with normal saline by shaking, but without crushing or macerating the mat, so as to remove traces of medium. The mat is then washed successively (three times) with 95 per cent alcohol. The washings are filtered and any residue which is carried over is collected on the filter paper and added to the mat mass. The bulk of mold is then placed in a vacuum desiccator containing $CaCl_2$ and is allowed to dry for one week.

After desiccation the mold is pulverized by grinding in a sterile mortar and pestle. A small quantity of mold is inoculated into broth and incubated. If the mold has not been killed it is treated with successive acetone washings and is again dried as described above.

The dried sterile mold is then extracted with alkaline buffered saline (Coca's) in the proportion of 3 grams to 100 ml. Extraction is carried out for two days. Filtration, concentration, sterilization and standardization are carried out as described in pages 522 to 533.

Preparation of Oil Extracts

Wherever a plant oil is the cause of a contact dermatitis, the following procedures may be used to obtain the active excitant. Poison ivy, poison oak, poison sumac, tulip, chrysanthemum, primula, juniper may thus be extracted; these procedures may also be employed in obtaining pollen oils from ragweed, timothy, etc.

The freshly collected leaves, as of poison ivy, are carefully freed of twigs and injured leaves which may be partly oxidized, placed in an oven at a low temperature, 40 to 50° C., overnight if necessary, until the leaves though remaining green become quite brittle and friable. They are then rubbed through a coarse meshed sieve, the midribs and stems discarded, and the coarse leaf meal stored in dry sealed glass containers containing silica gel. Thus kept, the leaf meal retains its activity indefinitely.

The alcoholic ivy extract which is in general use was originally described by Spain and Cooke.[21] The concentrated extract is prepared by allowing 10 grams of leaf meal to stand for twenty-four hours at room temperature in 100 ml. of absolute alcohol (any moisture such as present in 95 per cent alcohol permits oxidation, hence deterioration). No moisture or alkali must be present in any utensil. After paper filtration the extract is stored, no sterilization being necessary. Such extracts for use are diluted 1:2, 1:5, 1:10, 1:100, 1:1000 in absolute alcohol. Immediately before injection one part of these extracts must be diluted in a sterile syringe with nine parts of sterile salt solution, thus averting the pain which a stronger alcoholic extract would cause.

A preparation of the poison ivy leaf or like plant parts was described by Caulfeild[22] who used sterile Mazola (corn) oil. The residue from the ether-soluble fraction of the poison ivy plant was taken up in sterile Mazola oil. Serial dilutions from 1:10 to 1:10,000 (or concentrated, 10 per cent, 1 per cent, 0.1 per cent to 0.01 per cent) based on dilutions of the undiluted 1:10 or stock concentrated resinous solution with sterile corn oil were made. No dilution standard from the original weight of the plant leaf used for the extraction was made as is the case in the alcoholic and alum-precipitated pyridine-ivy extracts.

The degree of sensitiveness determining the dosage of the poison ivy extract in corn oil is determined by patch test with the alcoholic ivy extracts, since the oily ivy material does not lend itself to accurate skin testing. This procedure is used in the Roosevelt Hospital Allergy Clinic.

Alum-precipitated pyridine-ivy complex suspended in aqueous solution has been reported recently by Strauss and Spain.[23] This "extract" is much easier to handle and administer than the alcoholic or oily preparations. It is prepared as follows:

Ten grams of poison ivy meal (as described previously) are added to 100 ml. of pyridine. This mixture is allowed to stand for twenty-four hours in the ice box, and the leaf meal is then filtered off by means of a Buchner funnel. This pyridine-ivy stock solution is bottled.

To a 250 ml. sterile centrifuge cup are added 100 ml. of sterile distilled water and 40 ml. of pyridine-ivy stock solution. This is mixed well and immediately thereafter 40 ml. of sterile 0.25 N sulfuric acid solution containing 2 per cent potassium alum by weight are added slowly with shaking. A finely divided deep green precipitate results. After mixing thoroughly, the centrifuge tube is capped with a sterile rubber stopper and allowed to stand for twenty-four hours in the ice box.

The tube is then centrifuged and the supernatant fluid removed by means of a 100 ml. volumetric pipet containing a suction bulb attached at the end.

Then 200 ml. of sterile normal saline containing 0.4 per cent phenol are added. A sterile rod or pipet is introduced and the alum-ivy precipitate is mixed thoroughly with the saline. It is again centrifuged and the supernatant wash solution is discarded. A total of four 200 ml. sterile saline washings are made. Then sterile normal saline containing 0.4 per cent phenol is added to bring the volume up to 40 ml., that of the original volume of the pyridine-ivy stock solution. Sterility tests are run on this extract before use.

Care must be taken to mix the solution completely before making dilutions so as to obtain an homogeneous sampling. Dilutions of 1:5, 1:50, 1:100 and 1:500 are made with the above diluent or with sterile buffered saline.

This alum-precipitated pyridine-ivy "extract" is injected subcutaneously without any further diluting and is painless upon injection, in contrast to the oily ivy preparation which must be injected intramuscularly and the alcoholic ivy extract which must be diluted in saline solution each time immediately before use.

In all stages of preparation of poison ivy extract the susceptible worker must protect himself against the material.

Preparation of Various Extracting Fluids

1. Buffered saline *p*H 7.0 suggested by A. Evans.[10]

Stock I	
Potassium phosphate (KH_2PO_4)	3.63 or 18.15 gm.
Sodium phosphate ($Na_2HPO_4 \cdot 12\ H_2O$)	14.31 or 71.55 gm.
Sodium chloride (NaCl)	50.00 or 250.00 gm.
Distilled water (to make 1000 or 5000 ml.)	970.00 or 4850.00 ml.
Stock II	
Phenol 4%	

Combine equal parts of Stock I and Stock II. To one part of this mixture add four parts of distilled water.

Since large quantities of buffered saline are used in the laboratory, 5 liters of Stock I solution are made at a time and an amount sufficient to fill a 2 gallon jar is made of the final solution.

To make 7500 ml. of buffered saline add

750 ml. Stock I
750 ml. Stock II
6000 ml. distilled water
7500 ml. total volume of buffered saline

The above procedure is simplified in the laboratory by having a line etched on the glass jar at the 7500 ml. capacity. Add to the jar 750 ml. of Stock I, 30 ml. of concentrated phenol (since 750 ml. of 4 per cent phenol contains 30 grams of phenol), and distilled water to fill the jar to the 7500 ml. mark, and mix. Great care should be taken in handling the phenol, which is highly caustic and poisonous. It is heated in a water bath to liquefy and a cloth or tongs should be used in handling the phenol flask when pouring it into a graduated cylinder. *Never Pipet!*

2. Concentrated buffered saline (a five-fold concentration of the above). Use the same Stock I and Stock II as described for the regular buffered saline but combine equal parts of Stock I and Stock II for use without any further dilution.

3. Alkaline extracting fluid *p*H 8.2 described by Coca.[9]

Sodium chloride (NaCl)	0.5%
Sodium bicarbonate ($NaHCO_3$)	0.275%
Phenol (C_6H_5OH)	0.4%

4. Buffered sodium formaldehyde sulfoxylate extracting fluid pH 7.4 described by Strauss and Spain.[11]

Potassium acid phosphate (KH_2PO_4)	2.725 gm.
1 normal sodium hydroxide	15.73 ml.
Sodium formaldehyde sulfoxylate	10.00 gm.
Distilled water to make	1000.00 ml.

Approximately normal NaOH is made by diluting 59 ml. of concentrated NaOH (1:1 described in Appendix 5) to one liter with water and is standardized against standard acid.

5. Concentrated sodium formaldehyde sulfoxylate extracting fluid (a five-fold concentration of the above).

Potassium acid phosphate (KH_2PO_4)	13.62 gm.
1 normal sodium hydroxide	78.65 ml.
Sodium formaldehyde sulfoxylate	50.00 gm.
Distilled water to make	1000.00 ml.

Cleaning and Sterilization of Equipment

Cleaning. New glassware should receive special attention to render it free from resistant spores present in straw and packing material. Such spores resist hot-air sterilization but are destroyed by boiling the glassware in a strong soap solution (5 per cent) for one hour. Shavings of a good brown soap prevent the clouding on the glass produced by many soap powders.

Pipets are cleaned by first removing the cotton plugs and then placing in a large glass or stainless steel cylinder so that they stand on end. Water enters the jar continuously from the top and a siphon tube leaves the jar through a circular hole through the side about 1 inch from the top. A tight-fitting rubber stopper makes the connection between the siphon tube and jar airtight. In this way the pipets are continually flushed and emptied with water, since as soon as the level of the in-flowing water reaches the height of the siphon tube the water immediately starts to drain out of the jar and continues to siphon off until the level of the water is just below the end of the siphon, allowing air to enter the tube which prevents further siphoning until the jar is again completely filled. The diameter of the siphon tube should be large enough to permit the removal of the water, once the siphon is working, at a faster rate than that of the in-coming water. The pipets are rinsed several times with distilled water after coming from the washer and are then dried in an oven. Sulfuric acid-dichromate cleaning solution is used to clean out the pipets when they become very dirty or when water does not drain out evenly.

The rubber caps are not removed from the emptied used vials until a large enough batch has accumulated for washing. This eliminates the possibility of any extract drying up in the vial. The vials are boiled in soapy water and it is important that they be rinsed in dilute HCl to remove all traces of soap, as the acid is readily removed in several washings of water. The vials are all rinsed several times with distilled water before they are dried.

All new rubber caps and solid rubber stoppers are boiled for thirty minutes in dilute alkali and are then boiled for half an hour in two successive washings of distilled water. They are then rinsed under running tap water for at least fifteen minutes and thoroughly rinsed with distilled water.

Sterilization. Clean dry pipets are plugged with cotton at the upper end. A cylindrical metal case is filled with the pipets and its fairly tight-fitting cap is secured. Test tubes are plugged with cotton or non-absorbent cotton batting. Clean petri dishes are wrapped in paper or placed in special metal containers. Pipets, petri dishes and test tubes are sterilized by hot air in a gas or electrically heated oven in which the temperature should be kept between 160 to 170° C. for at least one hour.

Steam under pressure is the most powerful method of heat disinfection. It is always used to sterilize contaminated apparatus. Exposure to steam under 20 pounds of pressure for thirty minutes is sufficient to kill all forms of bacterial life including spores. The temperature attained by 15 pounds pressure is 121° C. and by 20 pounds pressure is 126° C. Caution must be taken to permit all air to escape from the autoclave before closing the vent. If this is not done a poorly conducting air pocket may be left about the objects to be sterilized and these may not be heated to the temperature indicated by the pressure. The following articles are sterilized by autoclaving:

Clean dry Pyrex nursing bottles (4 and 8 oz.) are plugged with a stopper made of cotton surrounded by Patapar paper. A small square of Patapar is then used to cover the stopper and lip of the bottle and is secured with string.

Seitz and Berkefeld filters are completely assembled and attached to the filter flasks. The side arm of the flask is plugged with cotton and the connection between the flask and the rubber stopper of the filter is carefully wrapped with a clean cloth, one lap of the cloth also covering the side arm of the filter flask. This cloth is secured with a couple of straight pins.

The clean rubber caps (for use on the 10 ml. vials) and solid rubber stoppers (for use in the nursing bottles) are placed in pint preserving jars and the space in the jars is filled with buffered saline or a 0.4 per cent solution of phenol. The rubber washer and glass top are secured with the top metal bar, the side bar being left loose in the upper position. After sterilization and after the jars have cooled somewhat, the side bar is clamped down making the jar airtight. The pressure would cause the jar to break if it were sealed during the sterilization.

The clean 10 ml. vials are placed in aluminum pans top down and the aluminum overlapping lid of the pan is secured with string or metal clamps.

Routine Testing Series

(As Used in the New York Post-Graduate Hospital Allergy Clinic)

POLLENS (Tested in 10, 100 and 500 unit (P.N.) strengths)

Ash
Beech
Birch
Elm
Hickory
Oak
Poplar
Timothy and Orchard*
Plantain
Ragweed†

Series 1—Weak Inhalants

Timothy and Orchard 100
Plantain 100
Ragweed 100
Dust Concentrate
Rabbit Epithelia 100
Feathers‡ 100
Orris 100
Cottonseed 100
Tobacco 100
Dog Epithelia 100
Horse Epithelia 100
Cat Epithelia 100
Horse Serum 1–100
Pyrethrum 100
Kapok 100
Flaxseed 100
Alternaria 100
Aspergillus 100
Penicillium 100
Hormodendron 100

Series 2—Strong Inhalants

Timothy and Orchard 500
Plantain 500
Ragweed 500
Dust Concentrate
Rabbit Epithelia 1,000
Feathers 1,000
Orris 1,000
Cottonseed 1,000
Tobacco 1,000
Dog Epithelia 1,000
Horse Epithelia 1,000
Cat Epithelia 1,000
Horse Serum 1–10
Pyrethrum 1,000
Kapok 1,000
Goat Epithelia 1,000
Alternaria 1,000
Aspergillus
Penicillium 1,000
Hormodendron 1,000

Series 3—Foods

Milk 1,000
Egg 100
Wheat 3,500
Rice 3,500
Rye 3,500
Oats 3,500
Chicken 3,500
Pork 3,500
Lamb 3,500
Beef 3,500
Codfish 100
Halibut 100
Tea 3,500
Coffee 3,500
Chocolate 3,500
Mustard 50
Coconut 100
Peanut 100
Pecan 100

Series 4—Fruits and Vegetables

Orange 3,500
Grapefruit 3,500
Peach 3,500
Prune 3,500
Apple 3,500
Strawberry 3,500
Banana 3,500
Onion 3,500
White Potato 3,500
Cabbage 3,500
Corn 3,500
Spinach 3,500
Cucumber 3,500
Lima Bean 3,500
Pea 3,500
Tomato 3,500
Celery 3,500

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* Timothy and orchard extracts are not tested or used for treatment separately but are combined in equal volumes of the same concentration. For example, 5 ml. of 100 unit timothy and 5 ml. of 100 unit orchard are combined to give 10 ml. of a 100 unit timothy and orchard extract.

† High and low ragweed extracts are made separately and then combined in equal volumes of the same concentration for the regular ragweed extract used in testing and treating.

‡ The feather extract is made up of equal parts of the same concentration of chicken, duck and goose epithelia.

Gelatin-Epinephrine and Gelatin-Pollen Extracts

A 1:500 gelatin-epinephrine mixture was described by Spain, Strauss and Fuchs.[24] This preparation is slowly absorbed, non-toxic, non-antigenic and is readily administered by the patient. A sharp reduction in the daily number of required doses of epinephrine is noted when this preparation is substituted for the aqueous solution. Marked clinical improvement frequently results.

The preparation is made as follows: To a solution containing 140 ml. of glycerin and 540 ml. of distilled water are added 7.2 grams sodium chloride, 4.0 grams chlorobutanol, 1.0 gram sodium bisulfite, and 160 grams powdered U.S.P. gelatin is added last. The preparation is mixed well, heated to dissolve the gelatin, and filtered through a Buchner funnel to remove any insoluble particles. This quantity of gelatin mixture is placed in a 2 liter Florence flask since the mixture tends to boil over if sterilized in too small a container. The gelatin mixture is sterilized by autoclaving for ninety minutes at 20 pounds pressure. Aerobic and anaerobic cultures are made and kept at 37° C. for four days before the sterility of the mixture is passed upon. This gelatin mixture remains stable for months.

The 1:500 gelatin-epinephrine is made by adding to four parts of the above sterile gelatin mixture, one part of a solution of 1:100 epinephrine hydrochloride. Aseptic precautions must be followed when the epinephrine is added and in the subsequent method of bottling. If the gelatin mixture is kept in the refrigerator it must be warmed in hot water to liquefy the gelatin so that it may be pipeted accurately. This 1:500 gelatin-epinephrine is dispensed in sterile brown bottles to protect the epinephrine from oxidation.

Spain, Fuchs and Strauss[25] have also used this gelatin mixture in combination with various aqueous pollen extracts for the treatment of patients so sensitive as to accept poorly the usual aqueous pollen therapy. A greater tolerance for the slowly absorbed gelatin-pollen extract was noted and higher maximum doses were given safely with half the usual number of injections and more effective clinical relief. Constitutional reactions were milder and their occurrence less frequent.

The gelatin-pollen mixture is made by adding to four parts of the above sterile gelatin mixture, one part of sterile aqueous pollen extract. The aqueous pollen extract is thus diluted five times. If, for example, a 5000 unit gelatin-ragweed extract is desired, then to 4 ml. of gelatin mixture must be added 1 ml. of 25,000 unit ragweed extract. A 50,000 unit pollen extract is necessary for a 10,000 unit gelatin-pollen extract. We have found that at least 50,000 unit pollen extracts are readily obtained by extracting 11 grams of pollen in 100 ml. of alkaline buffered sodium formaldehyde sulfoxylate extracting fluid.[11]

Sterilization of Small Quantities of Serum

Small quantities of serum, used in passive transfer skin tests, would be absorbed almost completely by the filter pad of a regular 25 ml. capacity Seitz filter cup leaving very little serum for the test. The Swinny filter adapter[26] is valuable in filtering small quantities of material. It is essentially a micro Seitz filter consisting of two metal parts of an adapter which screw together, packing tightly the metal screen, small half-inch asbestos filtering pad and rubber washer. It is placed in a large test tube plugged with cotton and is easily sterilized in the autoclave. The material to be filtered is placed in a Luer-Lok syringe (2 to 10 ml. capacity). A three ring Luer-Lok syringe is easier to operate. This syringe is then locked onto the sterilized Swinny filter adapter. The two parts of the adapter are rescrewed as tightly as is possible with the hands. Firm hand pressure is applied to the syringe forcing the solution through the filter and into a sterile vial. It must be remembered that even this small half-inch pad shrinks appreciably when wet. It is important to force only 0.1 ml. of serum from the syringe to wet the pad and then the two parts of the adapter are rescrewed to tighten the pad in place. Otherwise, the material to be filtered will slip through the edges and a sterile filtrate may not be obtained.

Serum which has been sterilized may be kept at ice-box temperature for many months without lessening its skin sensitizing properties.

Appendix

1. Allergens extracted with alkaline extracting fluid (Coca's[9])

Pollens: To obtain at least a 20,000 unit extract, the following weights of pollen are used per 100 ml. of extracting fluid

Beech, birch, poplar	8 grams
Ash, elm, oak, hickory	5 grams
Timothy, orchard, ragweed	4 grams
Plantain	6 grams

Fungi: 3 to 5 grams of dried powdered fungi per 100 ml.

Dust: Only sufficient extracting fluid to moisten

2. Allergens* extracted with buffered saline (sufficient to cover with exceptions noted)

Apricot
Barley (1 gm.:5 ml.)
Beans (lima, string)
Broccoli
Brussels sprouts
Carrots
Cauliflower
Corn
Cornmeal (1 gm.:5 ml.)
Epithelia
Fig
Horse radish
Nuts (1 gm. (dry, defatted): 10 ml.)
Okra
Oyster plant
Parsley
Parsnip
Pea (green)
Pumpkin
Rice (1 gm.:5 ml.)
Silk
Soybean meal (1 gm.:5 ml.)
Squash
Turnip

* Epithelia (cat, dog, chicken, etc.) are listed as a group and not separately.

3. Allergens extracted with concentrated buffered saline (to 4 parts of juice add 1 part of concentrated buffered saline)

    Cabbage
    Cantaloupe
    Cucumber
    Currant
    Garlic
    Gooseberry
    Grape
    Grapefruit
    Honeydew melon
    Lemon
    Lime
    Onion
    Orange
    Pineapple
    Rhubarb
    Tangerine
    Tomato
    Watermelon
    Watercress

4. Allergens* extracted with buffered sodium formaldehyde sulfoxylate fluid (sufficient to cover except where otherwise indicated or marked with "J." "J" signifies juicy; to 4 parts of juice add 1 part of concentrated sulfoxylate fluid)

    Alligator pear
    Apple—J
    Artichoke
    Asparagus—J
    Banana
    Bean (Navy)
    Beet
    Blackberry—J
    Blueberry—J
    Buckwheat (1 gm.:5 ml.)
    Celery—J
    Cherry—J
    Chocolate (1 gm.:5 ml.)
    Coffee (1 gm.:5 ml.)
    Cottonseed (1 gm.:10 ml.)
    Cranberry
    Dandelion—J
    Date
    Eggplant—J
    Endive—J
    Fish (1 gm. (dry, defatted):10 ml.)
    Flaxseed (1 gm.:20 ml.)
    Huckleberry
    Kapok seed (1 gm.:10 ml.)
    Lettuce—J
    Meats (1 gm. (dry, defatted):10 ml.)
    Mushroom
    Oats (1 gm.:5 ml.)
    Olives (green & ripe)
    Orris (1 gm.:5 ml.)
    Peach—J
    Pear—J
    Pepper (green & red)
    Plum—J
    Potato (sweet & white)
    Prune
    Pyrethrum (1 gm.:5 ml.)
    Radish
    Raisin
    Raspberry—J
    Rye (1 gm.:5 ml.)
    Spices (1 gm.:5 ml.)
    Spinach—J
    Strawberry—J
    Tea (1 gm.:5 ml.)
    Tobacco
    Vanilla
    Wheat (1 gm.:5 ml.)

5. Reagents and solutions used in the Kjeldahl nitrogen determination:

    Reagents used for the precipitation of protein as described by Cooke and Stull[19]

    A. 10% phosphotungstic acid in 10% concentrated hydrochloric acid
    10 grams of phosphotungstic acid made up to 100 ml. with 10% HCl

    B. Concentrated HCl.

    C. Acid wash solution containing 100 ml. of buffered saline, 25 ml. of concentrated HCl and 10 ml. of phosphotungstic acid solution.

    Reagents used for the macro Kjeldahl determination

    A. Digestion mixture
    2126 ml. concentrated H_2SO_4 (C.P.)
    1624 ml. concentrated H_3PO_4 (C.P.)
    1250 ml. 3% $CuSO_4$

    B. 10% ferric chloride solution

    C. Concentrated NaOH solution—technical
    Mix in a large enamel pail, 20 pounds of sodium hydroxide flakes, technical,† with 9225 ml. of distilled water. Stir until all of the sodium hydroxide has dissolved, cover the pail with a lid and allow to stand for two weeks so that the carbonate may settle out. The clear solution is siphoned off and stored in rubber-stoppered bottles.

    D. Methyl red-methylene blue indicator as suggested by Johnson and Green[27]
    Dissolve in 1000 ml. of 95% alcohol
    methyl red 1.250 grams
    methylene blue 0.825 grams

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* Meats and fish are listed in groups and not separately.

† Conveniently obtained in 10 pound hermetically sealed cans.

Preparation of standard alkaline and acid solutions

A. Concentrated NaOH solution (C.P.)

Combine equal quantities of NaOH pellets (C.P.) and distilled water and mix. Allow the solution to stand in a rubber-stoppered tall cylindrical jar for two weeks to clarify.

B. 1/14 N Potassium acid phthalate is the primary standard used in standardizing the NaOH to exactly 1/14 N.

Weigh accurately 1.457 grams of potassium acid phthalate (C.P.) and transfer to a 100 ml. volumetric flask and make up to the mark with distilled water and mix. This solution is exactly 1/14 N.

C. 1/14 N NaOH solution

Dilute 4.2 ml. of the clear concentrated NaOH (C.P.) to one liter for approximately 1/14 N NaOH. Into a clean Erlenmeyer flask introduce 20 ml. of 1/14 N potassium acid phthalate measured from an accurate clean pipet. Add 2 or 3 drops of a 1% alcoholic solution of phenolphthalein. From a buret run in the approximately 1/14 N NaOH until the last drop changes the colorless solution to a definite pink. Two duplicate readings should be obtained.

$$\text{The 1/14 N factor for the alkali} = \frac{\text{ml. of 1/14 N acid phthalate}}{\text{ml. alkali}}$$

If the factor is greater than one it indicates that the alkali is too strong. The remaining stock of alkali can be made exactly 1/14 N by diluting the total volume to the factor times that volume. After the alkali has been rediluted, its normality is rechecked by another titration which should now neutralize an exactly equal volume of potassium acid phthalate.

D. 1/14 N HCl solution

Dilute 6.07 ml. of concentrated HCl to one liter with water for approximately 1/14 N HCl.

Titrate 20 ml. of this solution against the standard 1/14 N NaOH using phenolphthalein as indicator in same manner as described above for the alkali standardization.

$$\text{1/14 N factor for acid} = \frac{\text{ml. of 1/14 N NaOH}}{\text{ml. of acid}}$$

The total volume of acid is then diluted to the factor times the volume of acid.

6. Preparation of media for anaerobic and aerobic culture

A. Wadsworth's[29] (Standard Methods 1939) cooked meat medium for anaerobes is used. To one part of lean ground beef add one part of distilled water and stir thoroughly. Heat slowly in a water bath to 95° C., stirring frequently. Place over a free flame and bring to boiling point, stirring constantly. Cool in an ice bath and skim off all fat. Filter a few milliliters of the medium through filter paper for use in testing the *p*H. Adjust the bulk of the medium to *p*H 8.0 with 5 N NaOH using 0.04 per cent phenol red as indicator and making color comparisons with standard buffers. Filter a final small amount of medium and recheck the reaction. Strain the medium through a sieve until the meat is comparatively dry. Place the meat in a funnel with a short wide stem and tube the meat in 150 × 15 mm. tubes by pushing it through the stem of the funnel by means of a glass rod. Fill tubes to depth of 25 to 30 mm. with the meat, then add the liquid to the same depth above the meat, by means of an ordinary tubing funnel. Sterilize by autoclaving at 20 pounds for twenty minutes. Sterilize petrolatum by dry heat for at least one hour at 165–175° C. After the media has cooled sufficiently to handle, place a petrolatum seal over the media in each tube.

B. Aerobic meat extract broth is very easily made and suffices for ordinary routine aerobic sterility tests. To one liter of tap water is added 5 grams of Liebig's meat extract, 10 grams of peptone and 5 grams of sodium chloride. The ingredients are mixed together in a Pyrex flask and heated over a free flame until the peptone and meat extract are dissolved. The medium is adjusted to *p*H 7.6 (with 1 N NaOH) since the heat of autoclaving usually increases the acidity of the medium reducing the *p*H to 7.4, which is the optimum for most pathogenic bacteria. The medium is titrated by the colorimetric method using standard buffers of known *p*H as controls and phenol red or bromthymol blue as indicators. This procedure is described in detail by Zinsser and Bayne-Jones[28] and other standard texts.

C. Dehydrated thioglycollate medium can be obtained from the Baltimore Biological Laboratory. It contains:

Pork infusion solids	1.0%
Peptone (thio)	1.0%
Sodium chloride	0.5%
Sodium thioglycollate	0.1%
Agar	0.05%
Dextrose	1.0%
Methylene blue	0.0002%

Sodium thioglycollate is a reducing agent and good anaerobic conditions exist in all but the upper portion of the medium. It is, therefore, possible to culture aerobes and anaerobes in this media.

Brewer's[13] thioglycollate medium is easily made by dissolving 3.65 grams of the powdered medium in 100 ml. of distilled water. The solution is heated to boiling and allowed to boil for one minute. It is tubed in 15 ml. amounts in 6 × ¾ inch test tubes. No adjustment of *p*H is necessary. It is autoclaved for twenty minutes at 20 pounds pressure and stored at room temperature. This medium is much easier to make and handle than the cooked meat media above described, and seems to support the growth of aerobes and anaerobes as well if not better than either of the previously mentioned media.

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APPENDIX

Non-Specific Causes or Influences in Relation to Allergic Disease

ROBERT A. COOKE

The human body is such a highly developed and integrated organism that all influences directly or indirectly affecting tissue or organ activities and functions may play roles of greater or less significance either in developing or in modifying the evidences, that is the signs and symptoms, of any disease.

All symptoms of allergic disease, be they nasal, bronchial, intestinal or dermal, may be produced or simulated by non-allergic disease. For the sake of accuracy in the pathogenic, etiologic and symptomatic study of disease, its diagnosis or management, a critical attitude must be maintained in evaluating the significance of non-specific factors, as for example, psychic, endocrinic or nutritional; that is, are they important from the standpoint of pathogenesis or etiology or are they merely contributing or modifying elements and thus secondary rather than primary elements in the disease? Many such factors appear in the course of any and especially chronic diseases be they allergic or otherwise. This is certainly true with regard to mental states and nutrition. Too often in diagnosis these non-specific factors are emphasized as causes without due regard to the possibility that they are results or are purely coincidental.

Psychic and Nervous Factors. There has been recently a revival of interest in psychic and nervous factors in relation to disease—so-called psychosomatic medicine. Claims are being made that dyspnea, diarrhea, indigestion and other symptomatologies, diagnosed as asthma, colitis, and the like, and assumed to be allergic, are caused by psychic factors and are curable by therapy based on this hypothesis. The idea has been put forth that psychic stimuli might bring about a release of histamine just as is presumed for antigen-sensitized cell reaction (allergy). For this however, there is no factual evidence. No one should belittle the importance of psychic influences upon body function in health and disease, but in so far as genuine allergy is concerned, there is no evidence that they play any part either in the genesis of the sensitized state or directly in the reaction of sensitized cells in the presence of antigen. An abnormal psychic state unquestionably modifies the attitude of the patient to the allergic disease which, if prolonged, is a cause of the mental response rather than the effect of it. The medical textbooks of only a few years ago applied the term neuroses to what we now regard as diseases of allergy. The classical experiment of inducing hay fever by an artificial rose is an example of false observation that was accepted as fact by many generations of doctors. Psychic factors cannot produce an allergic state or its resulting reaction but they may modify the symptoms quite naturally and not infrequently are the result of chronic allergy.

The autonomic nervous system is the great regulating and coordinating mechanism of the body. Eppinger and Hess[1] in their monograph on vagotonia emphasized the importance of vagal over sympathetic impulses in asthma. To a certain extent their idea was based upon the contraction of bronchi (asthma) by vagus stimulation and the relief of asthma by adrenalin which activated the opposing sympathetics. With the advent of the sensitization basis for asthma and other allergic diseases interest in the vagotonic theory has waned, for it is now known that asthma is not so much the result of bronchospasm as of bronchoedema. Although vasomotor instability is common in the allergic, it is as often encountered in non-allergic disease. The relation of the autonomic system both sympathetic and parasympathetic should be studied anew in the light of present knowledge, for through its effect on circulation and on endocrine secretions and nutrition it must play a significant though secondary part in modifying the symptoms of allergic disease.

Nutritional Factors. Studies of the metabolism of allergic patients with and without active symptoms have brought out many suggestions that an abnormal state of metabolism is responsible for the allergy. Great attention has been paid to *calcium.* First the blood calcium was said to be low in allergy, and when this was disproved it was then claimed that the amount of ionized calcium was too low. When this was not verified the idea was put forth that the ratio of calcium to other bases as potassium and sodium was abnormal. Actually there is no evidence that there is any disturbed calcium metabolism or that calcium therapy by mouth or vein has any effect on any allergic reaction. The case is the same with regard to *potassium.*

The *acid-base balance* has been studied with the idea that there was a shift to the alkaline side. The work as presented has not been impressive. Loveless[2] did not find any evidence of lowered gastric acidity in allergic patients and acid therapy has not been beneficial in allergic disease. Ketogenic diets have not favorably altered the symptoms of allergy and the acidosis of enforced starvation in status asthmaticus does not indicate any alleviating effect. In general it may be said that if variations from normal exist they are more likely a result, not a cause of allergy.

States of malnutrition resulting from diets deficient in vitamins or protein may be of real importance. Certain vitamin deficiencies produce actual tissue change, as for example in pellagra, but there is as yet no established laboratory or clinical evidence that the allergic state and reaction are directly influenced by such deficiency states though they may favor intestinal absorption of unaltered allergen and so facilitate sensitization. Certainly deficiency states predispose to infection and favor its progress. It is in this sense that in a general way and indirectly a state of athrepsia may be significant. It is an unfortunate fact that many of the deficiency states discovered in allergic and supposedly allergic patients are directly traceable to the long continued use of improper allergy diets.

Vitamin C deficiency and ascorbic acid therapy respectively have been claimed as the cause and the cure of hay fever. This has been thoroughly disproved. Black[3] has found *vitamin K* therapy beneficial in urticaria and angioedema, especially cases with prolonged prothrombin time. I have not been able to verify this in a small series; however, my cases have had normal prothrombin time. *Vitamin* B_1 preparations when given orally or parenterally have produced definite allergic reactions but no such reactions have been observed from the ingestion of this vitamin as contained in foods.

Little is known of the effects of *protein deficiency* upon the development of sensitization or its direct effect or influence upon an allergic reaction. Protein deficiency leads to edema which is one of its early manifestations, and like avitaminosis may cause absorption of incompletely digested food allergens and also an increase of symptoms in those allergic edema reactions such as asthma and urticaria. Protein deficiency likewise lessens resistance to infection and so facilitates those sensitizations based upon bacterial allergy. No careful study has been made to disclose the existence or effect of protein deficiency in allergy, although newer knowledge of protein nutrition has been applied to many other diseases. From the viewpoint of diagnosis, the use of amino acid therapy opens a new approach especially in the cases of suspected food allergy. Hill[4] and Olmstead et al.[5] have reported on their use, and I have had occasion to use satisfactorily an intravenous preparation (Amigen) in a few adults with intractable asthma and severe generalized dermatitis. In spite of the fact that the protein hydrolysates are theoretically non-antigenic, one must be on guard with their use in allergic patients. One of mine with severe dermatitis developed definite urticaria on two occasions. Also witness the fact that nucleic acid, which is not antigenic in the sense that it can induce sensitization, has produced immediate local and constitutional reactions in ragweed-sensitive patients as shown by Winkenwerder.[6] This observation has been confirmed by Sherman.[7] The entire subject of the relation of nutrition to allergy needs further study.

Endocrine Factors. It is quite natural that consideration should be given to the secretions of the various ductless glands in relation to the diseases of allergy. Theoretically there are two possible modes of acting: (1) the direct effect of any endogenous secretion action as an allergen and (2) the pharmacologic or physiologic effect of over- or undersecretion of one or another gland.

(1) Allergy literature contains many inferences and suggestions implicating the hormones but to date nothing approaching sound evidence has appeared which warrants the assumption that any endogenous hormone can have a direct effect in stimulating allergic antibody or reacting with it. Riebel,[8] for example, reported premenstrual rhinitis from ovarian hormone. The evidence is based upon a "slight" cutaneous reaction on test and precipitation of symptoms following the injection of theelin. No controls are cited and the preparation used is not derived from human sources. One of my patients was given a progesterone preparation by mouth for a threatened abortion. After two tablets she developed a severe asthma requiring adrenalin. The patient was known to be very sensitive to horse serum and the hormone used was derived from pregnant mare's urine. That the source of the hormone is important is also borne out by the reactions to heterologous insulin in patients who have no comparable reaction to their own insulin. I have known this to occur in a non-diabetic patient after insulin injection. A skin reaction or the reproduction of an allergy by use of heterologous hormone is not sound evidence of an allergy to the endogenous product as inferred by Riebel[8] or by Zondek and Bromberg.[9]

(2) As to pharmacologic or physiologic effects of the hormones, there has been much surmise and assumption but little proof. The *adrenal gland* has been suspected on account of the effect of epinephrine injections in neutralizing allergic reactions of the wheal type, but there is no evidence of increased or decreased activity of cortical or medullary secretion in the allergic patient. The *thymus gland* has been implicated on account of the so-called "thymic asthma" which is due to the mechanical effect of the enlarged gland and not to any secretory effect. The *pancreas* does not seem to play any part in allergy. Neither under- or oversecretion has been blamed although diabetics do become allergic to injected insulin. In my observations diabetes is seen in allergic disease in about the same proportion one would expect from its general incidence. This is contrary to the usually expressed view.

Thyroid gland disturbances are frequently encountered in allergic patients. The enlarged gland may act mechanically to produce dyspnea. Neither hypo- nor hyperactivity appears to be etiologically related to allergy. One might expect allergies of the edema type to be increased by hypothyroid edema but I recall no case in which the administration of thyroid has materially affected the course of an allergy. On the contrary Graves' disease, in association with infective asthma, is a serious complication not infrequently seen. The difficulty appears to arise from the patient's vasomotor instability and lack of resistance rather than from any specific endocrine effect and this often continues even in those patients who have been successfully operated upon and whose metabolic rate is normal. *Pituitary* or *parathyroid* glands seem to have no effect upon allergic diseases.

The hormones of the *ovary* are frequently incriminated to explain allergies of all types on account of the cyclic variations in relation to menstruation and pregnancy.

Pregnancy and Menstruation. These deserve special consideration for there has always been speculation on the bearing of these states on allergy. Among our cases there are as many women who are better or free during pregnancy as there are those whose symptoms are worse at this time. It has not been possible to establish any causal connection between the endocrine factors during pregnancy and any of the usual allergies that may exist. Sensitization of the Rh negative mother and the increased dyspnea of the asthmatic patient are not of endocrinologic concern although of importance to the physician. I have never seen any of the allergic diseases excepting those related to the Rh factor either caused by or cured by pregnancy, although allergy of course frequently occurs. When a pregnancy either modifies or appears to cause an allergy, a satisfactory explanation can usually be found. For example, a patient who was pregnant developed urticaria. A careful history brought out the fact that the patient drank an excessive amount of milk. A superficial diagnosis blamed the pregnant state for the lesions which disappeared promptly when the allergen (milk) was omitted. In other patients it has been a cathartic such as senna, or some coal tar product.

The relation of the menstrual cycle to allergy is not so easily resolved and I have never observed a case in which I could be convinced of the etiologic role, though menstruation may accentuate the symptoms if there is any effect. This may be explained by the physiologic edema of the tissues generally which may thereby increase the symptoms of vasomotor rhinitis, asthma, urticaria or angioedema.

General Factors. Chief among these are physical exertion, fatigue, exposure to extreme cold, humidity and irritating fumes or gases, alcohol and tobacco. Any of these may incite a reaction which merely duplicates the specific allergy but this they cannot do in the non-allergic. In general then, all these factors may be regarded as excitants of an allergic type of response but only in those patients whose tissues have become habituated to that reaction as a result of true allergy.

Summary

(1) Psychic and nervous factors may simulate allergic disease but there is no proof that they produce a sensitization nor effect an allergic

reaction, although they undoubtedly are contributing and modifying factors.

(2) In the same way nutritional factors, vitamin and protein deficiencies, may be important in that they favor absorption of unaltered protein thus facilitating sensitization or, by the tendency to edema, accentuate allergic disease. They are never allergenic factors.

(3) In spite of the attempts to incriminate endogenous hormones as allergens, there is as yet no proof of their role. Increased or decreased amounts of hormones may act as pharmacologic or physiologic agents to modify existing allergic disease.

The variations of ovarian hormones that occur during menstruation and pregnancy actually have little effect on the course of allergic disease.

(4) Many general factors such as exertion, cold, humidity, alcohol and tobacco sometimes appear to act as excitants of allergic symptoms—actually they are effective only in those who are habituated to a response as a result of specific allergic reaction.

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